ORAL MUCOSAL MICROCIRCULATION IN THE CONTEXT OF ENDOTRACHEAL TUBE-RELATED PRESSURE ULCER DEVELOPMENT

A DISSERTATION SUBMITTED TO THE GRADUATE DIVISION OF THE UNIVERSITY OF HAWAIʻI AT MĀNOA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

NURSING

July 2018

By

Nicolle M. Chun

Dissertation Committee:

Alice Tse, Chairperson
Joyce Black
Bob Cooney
Scott Gallacher
Dan Milstein
Lorrie Wong

Keywords: oral mucosal microcirculation, oral mucosa pressure ulcer, endotracheal tube, nursing

Acknowledgements

I would like to express my deepest appreciation to my dissertation committee chairperson, Dr. Alice Tse, for her support and encouragement over the past two years. She took over the dissertation committee chairperson role at the very end of my journey. She gave me endless encouragement and guidance to meet my milestones.

I would also like to thank my committee members Dr. Dan Milstein, Dr. Joyce Black, Dr. Scott Gallacher, Dr. Lorrie Wong, and Dr. Bob Cooney for freely sharing their expertise and insights, and for their contributions to my writing.

I would like to thank my Queen's Medical Center, Medical Intensive Care Unit (MICU) Medical Director, Dr. Gallacher and Nurse Manager, Cheryl Fallon who believed in me to conduct this research study, helped me to obtain funding to borrow the equipment, and gave me encouragement and support throughout this academic journey. To my Queen's coworkers, you are my forever cheerleaders and gave me shoulders to cry on when I needed it. Many thanks to Gwen Isherwood, Queen Emma Nursing Institute, and Beth Freitas, The Queen's Medical Center, for reviewing and giving me insight to improve the flow of my manuscript. Thank you, MICU patients, who shared their time and allowing me to explain the importance of conducting bedside research to improve patient outcomes.

Last but not least, I would like to thank my family who tolerated my ups and downs and gave me endless support to complete this journey.

Abstract

Critically ill patients commonly require multiple medical devices such as cardiac monitors, ventilators, non-invasive positive pressure ventilators, nasal gastric tubes (NG), orogastric tubes (OG), and urinary tract catheters. Nurses are challenged to prevent hospital acquired pressure ulcers (HAPUs) because many of these devices can cause ulcers on bony prominences and mucosa. The literature indicates that medical device-related pressure ulcers (MDRPUs) associated with endotracheal tube (ETT) were the most frequent (Coyer, F., Stotts, N. & Blackman, V., 2014; Hanonu & Karadag, 2016), with highest rates of MDRPUs were observed among Medical Intensive Care Unit (MICU) patients (Hanonu & Karadag, 2016). The purpose of this study was to explore the effects of ETT pressure and ETT repositioning frequency on oral mucosa microcirculation among intubated patients to guide clinicians in the prediction and prevention of oral mucosa pressure ulcers (OMPrU).

A single-site, prospective, descriptive, observational study was conducted with a convenient sample of six patients who were enrolled between January 7, 2016 and June 30, 2016. Age, vital signs (including body temperature, heart rate (HR), mean arterial pressure (MAP)) , Sequential Organ Failure Assessment (SOFA) score, usage of anticoagulant, usage of pressor, total capillary density (TCD), functional capillary density (FCD), the percentage of perfused and non-perfused capillary loops (PPC) and microvascular flow index (MFI) were measured to address three research questions: What microcirculation changes of upper lip oral mucosa occur from ETT pressure every two hours upon ETT repositioning during the first eight hours of intubation using the ETT holder, AnchorFast?; What relationships exist between participants' vital signs and oral mucosal microcirculation?; What relationship exists between participants' age, SOFA score, and Braden Scale for Predicting Pressure Sore Risk (BSPPSR) and final 8-hour vital signs and final 8-hour oral mucosal microcirculation?

This study provides additional evidence to support current practice of ETT repositioning every 4 hours. Future research on oral mucosa microcirculation in context of ETT-related pressure ulcer prevention should address the relationship of oral mucosa microcirculation including other variables such as patients' underlying medical diagnoses, BSPPSR subscale, choice of sedation medication, gender, and angle of ETT.

Keywords: oral mucosal microcirculation, oral mucosa pressure ulcer, endotracheal tube

Table of Contents

Table of Contents (continued)

List of Tables

List of Figures

List of Abbreviations

ANOVA – Analysis of Variance

BP – Blood Pressure

BSPPSR - Braden Scale for Predicting Pressure Sore Risk

CC – CytoCam

EMR – Electronic Medical Record

ETT – Endotracheal Tube(s)

FCD – Functional Capillary Density

HOB – Head of Bed

HR – Heart Rate

ICU – Intensive Care Unit

IDF – Incident Dark Field

IRB – Institutional Review Board

MAP – Mean Arterial Pressure

MDRPU – Medical Device-Related Pressure Ulcer(s)

MV – Mechanical Ventilation

MICU – Medical Intensive Care Unit

MFI – Microvascular Flow Index

MPrU – Mucosal Pressure Ulcer(s)

MRN – Medical Record Number

NG – Nasogastric

NPUAP – National Pressure Ulcer Advisory Panel

OG – Orogastric

OMPrU – Oral Mucosal Pressure Ulcer(s)

PI – Primary Investigator

PPC – Proportion of Perfused Capillaries

PrU – Pressure Ulcer(s)

QMC – Queen's Medical Center

RCP – Respiratory Care Practitioner

RN – Registered Nurse

ROI – Region of Interest

SICU – Surgical Intensive Care Unit

SOFA – Sequential Organ Failure Assessment Score

TCD – Total Capillary Density

VAE – Ventilator Associated Event

VAP – Ventilator Associated Pneumonia

Chapter 1: Introduction

Disclosure

Although the study used AnchorFast® as endotracheal tube (ETT) securement, this research was not funded by its manufacturer, Hollister Incorporated.

Problem

Florence Nightingale recognized traditional pressure ulcers on bony prominences as a preventable injury and a nursing responsibility nearly two centuries ago (Nightingale, 1860). Pressure ulcers (PrUs) are defined as "any area of localized damage to the skin and underlying tissue caused by pressure, shear, or friction, or a combination of these actions" (Haessier, 2014). Critically ill patients are at high risk of development of PrUs due to their unstable medical condition and the invasive nature of the many interventions and therapies they receive (Tayyib, Coyer & Lewis, 2013). Critically ill patients commonly require multiple medical devices such as cardiac monitors, ventilators, non-invasive positive pressure ventilators, nasal gastric tubes (NG), orogastric tubes (OG), and urinary tract catheters. Critical care nurses are challenged to prevent hospital acquired pressure ulcers (HAPUs) because many of these medical devices are required to treat patients in intensive care units (ICU).

HAPUs pose a significant problem in elderly and critically ill patients by causing pain, decreasing quality of life, leading to significant morbidity, and prolonging hospital stays. In a study by the Institute for Healthcare Improvement (IHI, 2006), approximately 2.5 million patients are treated for pressure ulcers in US health acute care facilities each year. The estimated cost of individual patient care ranges from $20,900-$151,700 per pressure ulcer (IHI, 2006), and the total cost for treatment of pressure ulcers in the US healthcare system is estimated at $9.1-$11.6 billion per year (Berlowitz et al., 2014).

Mucosal pressure ulcers (MPrUs) are a relatively new phenomenon (National Pressure Ulcer Advisory Panel (NPUAP), 2008). Unlike traditional pressure ulcers which are localized injury to the skin and/or underlying tissue over bony prominences (www.NPUAP.org, 2014), MPrU occurs on mucosal membrane where no bony prominences are involved. In August 2008, the NPUAP recognized that pressure ulcers could occur not only over bony prominences but also on any tissue under pressure, especially from medical devices. The NPUAP released a position statement and defined that MPrUs are "found on mucous membranes with a history of a medical device, such as oxygen tubing, endotracheal tubes, bite blocks, orogastric and nasogastric tubes, urinary catheters and fecal containment devices, in use at the location of the ulcer" ("Mucosal Pressure Ulcers", 2011).

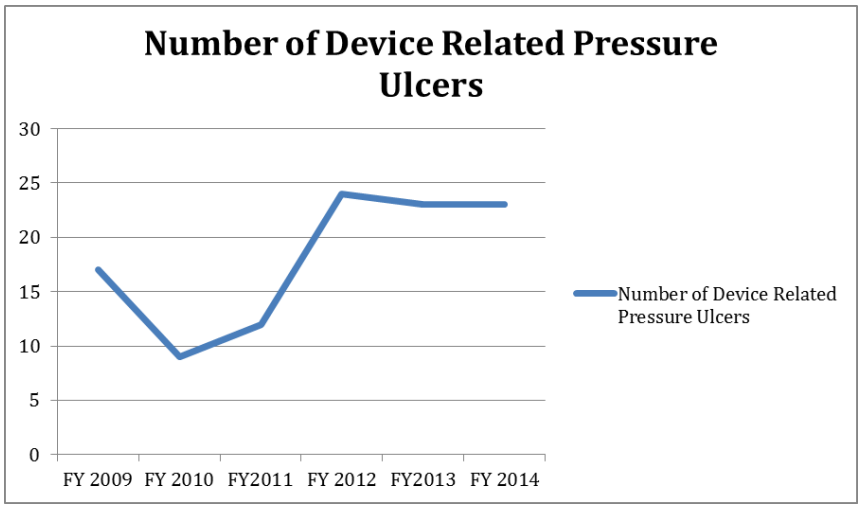
The majority of medical device-related pressure ulcers (MDRPUs) are oral mucosal pressure ulcers (OMPrUs) attributed to endotracheal tubes (ETTs) in critical care units. One of the risks of endotracheal intubation is the development of skin and oral mucosal pressure ulcers (OMPrUs) that result from direct pressure to inner oral mucosa and lips due to tight securement of the ETT over a period of time. In particular, OMPrUs have broad implications for the patient and the hospital. Negative outcomes include wounds requiring surgical intervention, increased risk of infection, increased length of stay, and patient body image disturbance. Liu et al (2010) study of 509 Chinese subjects found respiratory complications due to ETT in post-op patients including tracheal mucosa damage. In addition, laryngeal injury including inflammation and edema, mucosal ulceration, granulomas, vocal cord paralysis, and laryngeal tracheal stenosis are all complications associated with ETT placement (Hyzy, 2017). The new requirements for reporting nosocomial pressure ulcers have redefined the way we approach securing ETT and providing safe care (Hollister, 2013, p.2).

Specific Data Related to Medical Device Related Pressure Ulcers

MDRPUs have become more evident as traditional pressure ulcers are trending down (Apold & Rydrych, 2012), and patients with medical devices are 2.4 times more likely to develop a pressure ulcer of any kind than those without medical devices (Black et al., 2010). Among MDRPUs, OMPrUs are more frequent among adult critically ill patients. OMPrUs related to ETTs are found on labial mucus membranes of the upper or lower lip. Researchers have identified further systematic investigation is needed to determine how long any device can be in place before it needs to be moved or removed, and how often to examine the skin should be examined (Black et al., 2010).

An important quality indicator at the Queen's Medical Center (QMC) in Honolulu, Hawai`i is quarterly prevalence rates of HAPUs. Consistent with Black et al.'s findings (2010), numbers of MDRPUs have increased at QMC from 9 in fiscal year 2010 to 23 in 2014 (see Table 1).

Table 1. Number of Device Related Pressure Ulcers at QMC



Of the pressure ulcers reported at the QMC Medical Intensive Care Unit (MICU) and Surgical Intensive Care Unit (SICU) in December 2014, four HAPUs were identified, and all were MDRPUs. Two of these four MDRPUs were OMPrUs and resulted from ETTs; one resulted from a tracheostomy collar and the other resulted from a NG tube. Exploring the effects of ETT pressure on oral mucosa microcirculation and effects of ETT placement duration and reposition intervals will guide the development of practices that prevent OMPrU.

Significance

Pressure ulcers affect physical and psychosocial function and impose a financial burden on the patient's family and society (Wong & Stotts, 2003). Avoiding MDRPUs among critically ill patients is often more complicated than preventing those related to bony-prominences because the medical device is usually an essential diagnostic/therapeutic component of treatment (Fletcher, 2012).

The prevention of pressure ulcers has long been considered to be within the domain of nursing practice. Pressure ulcers may occur in spite of a proper position change regimen and meticulous nursing care. The nursing goal of eliminating external pressure to prevent pressure ulcers often translates as a failure of nursing care when patients develop pressure ulcers. Research has identified the interruption of soft tissue microcirculation as having a significant role in the development of pressure ulcers and the exact mechanisms still remain unclear (Tsuji, Ishioka, Sekiya & Nakatsuka, 2005).

Key Problem Area: Lack of Knowledge About Prevention of OMPrUs

Minimal research has been published on OMPrU prevention. Research on ETTs and other device-related OMPrUs has compared ETT securement with conventional tape and

holders. Kaplow and Bookbinder (1994) compared four ETT holders and standard method with tape. The study suggested that the SecureEasy holder was the preferred method for securing ETT for ETT stability, facial skin integrity, patients' and registered nurses' satisfaction compared to tape. A case study by Yamashita, Nishio, Daizo, Kishibe & Shimada (2014) reported that 2 patients developed an intraoperative PrU on the lower lip where an ETT was secured with polyurethane film for over 270 minutes during rhinoplasty. Nurses' anecdotal evidence on the difficulty of oral mucosal assessment and oral care using adhesive tape, inconsistent rotation of ETT position, and tightness of ETT securement, are important reasons to reassess the current practice of ETT management at QMC.

Studies on MDRPUs indicate that MDRPUs occurred more than non-MDRPUs among critically ill patients, and the most frequent MDRPU was ETT-related OMPrU (Black et al, 2010; Chun, 2014; Coyer, Stotts & Blackman, 2014; Hanonu & Karadag, 2016). Although awareness of MDRPUs on oral mucosa has increased, research on understanding oral mucosa changes due to pressure, friction and shearing from ETT is scant.

Chapter 1 Summary

Research literatures continues to suggest that MDRPUs have become more evident. As traditional pressure ulcers are trending down, patients with medical devices are 2.4 times more likely to develop a pressure ulcer of any kind than those without medical devices (Apold & Rydrych, 2012; Black et al., 2010). Despite the recent awareness of MDRPUs, and the fact that ETT-related OMPrU are the most frequent MDRPU, there is little research to guide nurses to prevent ETT-related OMPrU. Further research is essential to explore and better understand oral mucosal microcirculation in the context of ETT-related pressure ulcer development.

Chapter 2. Review of Literature

Introduction

Microcirculation is readily and frequently used by healthcare professionals, and its meaning is assumed to be clear and universally understood. However, the interpretation of microcirculation is uniquely personal due to the individuals' intrinsic and extrinsic factors and varies among different body parts. Microcirculation in the context of pressure ulcer development is a fundamental concept to understand the development of pressure ulcer "pathomechanically" and "pathophysiologically" because interruption of microcirculation plays a significant role (Tsuji et al., 2005).

OMPrUs in medical intensive care unit (MICU) are becoming more prevalent and require further exploration in terms of ETT placement, which causes mucosal membrane pressure injury. Further description of this phenomena is needed in order to develop preventive interventions to improve patient outcomes. The purpose of this literature review was to define microcirculation, describe ETT-related pressure ulcers, and describe several components of the labial mucosa: characteristics of the labial mucosa, physiological determinants affecting labial mucosa microcirculation and environmental determinants affecting labial mucosa microcirculation.

Literature Review

Literature was obtained using computerized searches of PubMed Medline, CINAHL, and Google Scholar for the years 1987-2016. Additional sources were obtained after reviewing the bibliographies of the literature identified by the initial search. The terms of 'device related pressure ulcers', 'endotracheal tube related pressure ulcer', 'microcirculation', 'upper lip', 'lips', 'labial mucosa', 'pressure injury 'and 'mucosal pressure ulcer' were used. These terms evolved from the reading of pressure relief research to optimize microcirculation to prevent pressure ulcers. Any references published in English or translated into English were included. Research studies on humans were included. This initial literature search covered 25 published reports on labial mucosa microcirculation.

Definition of microcirculation.

Microcirculation is a combination of words "micro" and "circulation" and the origin of these two words are from 1955 to 1960 (Dictionary.com Unabridged, 2010). Micro was derived from the Greek word "mīkrós" and is a combining form with the meaning "small". Circulation was derived from the Latin word "circulationem" from cirulare "to form a circle" "from circulus" and it was first used in relation to blood by William Harvey in 1628 (Online Ethymology Dictionary, 2010). Circulation is defined as a noun and is described as a) "an act

or instance of circulating, moving in a circle or circuit, or flowing"; b) "the continuous movement of blood through the heart and blood vessels, which is maintained chiefly by the action of the heart, and by which nutrients, oxygen, and internal secretions are carried to and wastes are carried from the body tissues"; c) "any similar circuit, passage, or flow, as of the sap in plants or air currents in a room"; d) "the transmission or passage of anything from place to place or person to person: the circulation of a rumor; the circulation of money"; e) "the distribution of copies of a periodical among readers"; f) "the number of copies of each issue of a newspaper, magazine, etc., distributed"; and g) "coins, notes, bills, etc., in use as money" (Dictionary.com Unabridged, 2010).

When these two words, "micro" and "circulation", are combined and used as one word, its meaning becomes more specific towards a scientific definition. As one word, microcirculation is described as "the movement of blood through the arterioles, capillaries, and venules" (Dictionary.com Unabridged, 2010). Other sources define microcirculation as a) "blood circulation in the microvascular system or the microvascular system itself" (Merriam-Webster's Medical Dictionary, 2007); b) "the flow of blood or lymph through the smallest vessels of the body, especially as the venules, capillaries, and arterioles" (The American Heritage Stedman's Medical Dictionary, 2002); and c) "the small vessels in the vasculature which are embedded within organs and are responsible for the distribution of blood within tissues" (Wikipedia, 2010). Microcirculation involves extremely small vessels (10-100 μm in diameter) (Wikipedia, 2010; Lipowsky, 2005; Tuma, Duncan, & Ley, 2008); innervated blood vessels (Wikipedia, Tuma et al., 2008); regulation of blood flow, tissue perfusion, blood pressure, tissue fluid, delivery of oxygen and other nutrients, removal of CO_2 , oxygen free radicals, and other metabolic waste products, body temperature (Lipowsky, 2005); and important role in inflammation (Trzeciak and Rivers, 2005)

In general, there is a tremendous amount of research done on pressure ulcers, starting with Kosiak's 1958 study. Recent pressure ulcer studies are evolving as they now examine the changes associated with superficial structures of the skin to much more complex structures, such as microcirculation of both skin and muscles (Salcido, Popescu & Ahn, 2007). Although a large body of knowledge exist on pressure ulcers, very few research studies on microcirculation in the context of pressure ulcers exists, as focus in this area did not start until the 1990's. "Given the magnitude of the problem, it is notable that there remains a paucity of research and a corresponding evidence base for our practices. Pressure ulcer research remains in its infancy" (Salcido et al., 2007).

ETT-related pressure ulcers.

The literature indicated that ETT-related MDRPUs were the most frequent (Coyer et al., 2014; Hanonu & Karadag, 2016) and the highest rates of MDRPUs were observed among medical ICU patients (Hanonu & Karadag, 2016). The retrospective study by Zaratkiewicz et al. (2010) showed that AnchorFast with Universal Bite Block decreased ETT-related mucosal pressure ulcers. Cooper (2013) also noted ETT pressure could cause pressure ulcers on a patient's lips, and failure to follow manufacturers' recommendations for endotracheal securement on appropriate patients (patients without facial edema, lip edema, protruding teeth) and repositioning ETT every 2 hours could lead to oral mucosa pressure ulcer.

Characteristics of labial mucosa.

The upper lip mucosa is defined as the inner aspect of the lips covering the maxillary jaw region and dentition. This region is called labial mucosa, which is one type of non-keratinized lining mucosa that has a softer texture, moist surface and ability to stretch and be compressed, acting as a cushion for the underlying structures (https://pocketdentistry.com/9-oral-mucosa/, 2015), and lips are pliable because of no bones and no infrastructure (Madhav & Ojha, 2012).

Scardina and Messina (2003) studied microcirculation of the lower lip in healthy subjects using computerized video-microscopic techniques that measured visibility of the capillary loops, orientation with respect to the surface, capillary density, capillary tortuosity, microhemorrhages, characteristics of the capillary loops, number of visible capillary loops in every square millimeter. These authors determined that the characteristics of the lower lip are composed of a network of capillaries in polygonal mesh and a parallel orientation with respect to the surface. The tortuosity of the capillaries (crossing of capillaries) are limited to the lip region. Furthermore, micro-hemorrhages were noticed in the lower lip mucosa that could have been possibly caused by microtraumas. Capillary loops have variable diameters, courses, and lengths, and have shapes like a horse stirrup, hairpins, commas and candle holders with multiple arms. Yu et al. (1994) also found that labial mucosa capillaries had a simple hairpin shape originating directly from the subpapillary vascular work.

Physiological determinants affecting labial mucosa microcirculation.

Age, body temperature, heart rate and blood pressure affect tissue tolerance for pressure and oxygen concentration changes (Keller, Wille, Ramshortst, & Werken, 2002). Bergstrom & Braden's (1992) study showed that older age subjects with lower systolic and diastolic blood pressure and higher body temperature developed pressure ulcers.

Nakagawa et al. (2011) found negative correlations between age and distensibility of the lower labial mucosa, and between age and moisture content of the lower labial mucosa. Scardina & Messina (2012) examined oral microcirculation of 27 women in pre and post menopause. The study showed post-menopausal women showed decrease in diameter of loops and increase in tortuosity in oral labial mucosa, which may indicate a greater permanence of inflammatory factors. Townsend et al. (2015) found that there was an increased influx of red blood cells (RBC) containing oxygenated hemoglobin flowing through the loop during systole, and this was more evident in the labial tissues. On imaging, the investigators propose that the dilated capillary loops and reduced oxygen exchange were determined to be associated with the development of longer capillary loops that lead to periodontal breakdown, and that this may possibly be an early sign of inflammation.

Systemic sclerosis, Sjogren's syndrome, burning mouth syndrome, and smoking showed evident alteration in the capillaries (Grassi et al, 1993; Scardina & Messina, 2004; Scardina et al., 2008; Scardina et al., 2009; Scardina et al., 2011).

Environmental determinants affecting labial mucosa microcirculation.

Retrospective studies were conducted to describe the human, product, and environmental factors that might contribute to MDPrUs. A retrospective study by Zaratkiewicz et al. (2010) showed that AnchorFast with Universal Bite Block decreased ETT-related mucosal pressure ulcers. However, the frequency of ETT positioning to prevent mucosal pressure ulcers was not addressed in the study. Cooper (2013) noted that repositioning of ETT every 2 hours by the manufacturer's recommendation was based on a patient turning schedule every 2 hours. According to the PI's personal communication with the manufacture of Anchor Fast's clinical scientists, the every 2-hour repositioning of ETT by the manufacturer's recommendation was not derived from evidence-based or a research-based recommendation. Other authors suggest research is needed on how long any device can be in place before it needs to be moved or removed (Black et al., 2010; Norman, 2013).

A study by Chun (2014) extracted data from the electronic medical record (EMR) during two different time periods: a) February 1, 2013 to March 9, 2013 (27 charts of intubated patients); and b) November 1, 2013 to December 9, 2013 (25 charts of intubated patients). However, a wide variability of prevalence rates was noted in June 2013 (15%) and December 2013 (0%). Findings showed higher usage of AnchorFast, fewer ventilator days, and improved nursing documentation about skin and oral care during November 1, 2013 to December 9, 2013. One patient developed OMPrU and used the ETT holder AnchorFast, but ETT repositioning was not done every 4 hours as per the QMC AnchorFast Guideline (see

Appendix 1). A finding from this study concurred with Zaratkiewicz et al's (2010) study, that the AnchorFast ETT holder decreased ETT-related OMPrUs; however, it also raises important questions about ETT repositioning frequency. Exploring and understanding microcirculation of upper lip oral mucosa related to securement and repositioning frequency in intubated patients will assist in the development of evidence-based practices designed to prevent ETT-related OMPrUs.

Limitations of the Existing Literature

No research was found that examines labial mucosa microcirculation in the context of pressure ulcer development from ETTs. A few studies (Cooper, 2013; Ozyurek & Yavuz, 2015; Zaratkiewicz, 2012) suggest that using AnchorFast helped to reduce oral mucosa pressure ulcer related to ETT use, however the frequency of ETT repositioning was not addressed by these authors.

Gaps in the Literature

There is evidence suggesting a relationship between the use of AnchorFast and the prevention of oral mucosa pressure ulcer from ETTs. However, no literature was found that examined the repositioning of ETTs on a sequential basis, such as every 2 hours, to prevent OMPrUs.

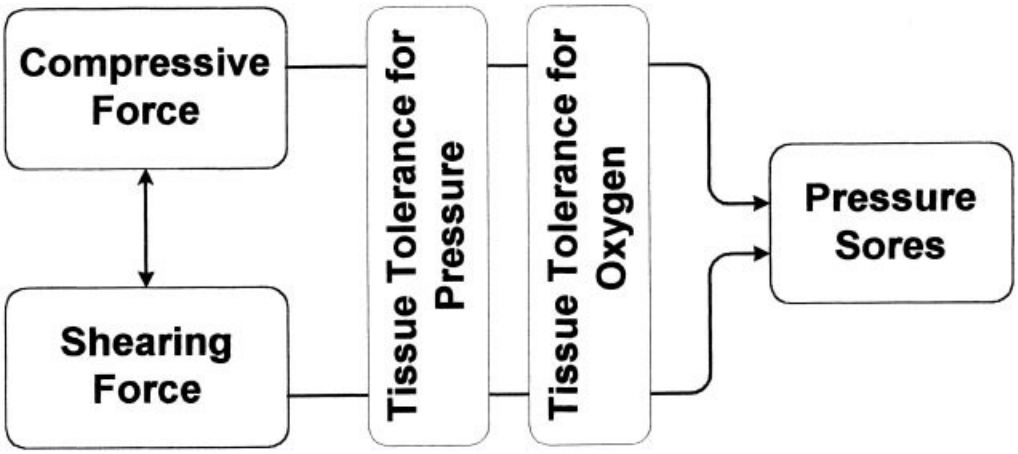
Purpose Statement

The objective of this study was to explore the effects of ETT pressure and ETT repositioning frequency on oral mucosa microcirculation among intubated patients with the aim to guide clinicians in the prediction and prevention of OMPrUs. This knowledge may inform clinician's knowledge in predicting and preventing OMPrUs.

Theoretical Model / Conceptual Framework

According to Defloor (1999), both compressive force and shearing force have an impact on pressure ulcer development. In his conceptual scheme model (Fig. 1), Defloor shows that these two factors affect tissue tolerance for pressure and oxygen that determine pressure ulcer development. Defloor's conceptual scheme is important in this study, as it can reveal both to what extent compressive force from ETT and shearing force from repositioning frequency of ETT changes in microcirculation of labial mucosa.

Figure 1. Defloor's concept scheme. From Defloor (1999). Reprinted with permission.



Compressive force.

Defloor (1999) described compressive force as a force exerted perpendicularly to the tissue, while shear is a force exerted parallel to the tissue, and "a pressure higher than the capillary pressure would slow down the flow in the capillaries and lymph nodes, resulting in insufficient supply of oxygen and nutrients and insufficient evacuation of metabolic waste" (p. 208-209). Intensity and duration of pressure from ETT would interfere flow in the capillaries, resulting in insufficient exchange of oxygen, nutrients and metabolic waste products.

Shearing force.

Defloor (1999) described shearing force as a force exerted parallel to the tissue, and this made perfect sense that shearing force from ETT repositioning could lead to stretching and micro-hemorrhaging from micro-trauma and possibly altering the papillary layer of the histology.

Tissue tolerance for pressure.

Defloor (1999) described tissue mass, age, dehydration, protein and vitamin C deficiency, corticosteroid, and stress would influence tissue tolerance. Nakagawa et al. (2011) studied age-related changes in the elastic properties and moisture content of the lower labial mucosa and found a negative correlation between age and distensibility of the lower labial mucosa and age and moisture content of the lower labial mucosa. This study supported that Defloor's concept scheme of tissue tolerance for pressure as one of factors. Age and moisture of labial mucosa could change the resilience and capacity of the tissue to redistribute pressure.

Tissue tolerance for oxygen.

Defloor (1999) stated that factors affecting oxygen supply such as fever, use of beta-blockers, malnutrition, tobacco use, reactive hyperemia, diabetes, and hypotension could affect tissue tolerance for oxygen. Although there were several research studies of labial mucosa microcirculation with previously mentioned factors, it is too early of a stage to conclude that local mucosa microcirculation could be a measurement of systemic conditions.

Chapter 2 Summary

Overall research on compressive and shearing forces from ETT affecting labia mucosa microcirculation is lacking. Since this study's aim is to describe changes of upper lip oral mucosa microcirculation related to ETT pressure and repositioning of ETT, Defloor's conceptual model may be used to explain the phenomena under study.

Chapter 3. Methodology

Purpose

The purpose of this study was to explore the effects of ETT pressure and repositioning frequency on oral mucosa microcirculation among intubated patients to guide clinicians in the prediction and prevention of OMPrU.

Study Aim and Research Questions

Aim: Describe changes of upper lip oral mucosa microcirculation in relation to ETT pressure and repositioning.

Research Question 1. What microcirculation changes of upper lip oral mucosa occur from ETT pressure every 2 hours upon ETT repositioning during the first 8 hours of intubation using the ETT holder, AnchorFast.

Research Question 2. What relationships exist between participants' vital signs (including body temperature, heart rate (HR), mean arterial pressure (MAP)) and oral mucosal microcirculation.

Research Question 3. What relationship exists between participants' age, SOFA score, and Braden Scale score and final 8-hour vital signs (including body temperature, heart rate (HR), mean arterial pressure (MAP)) and final 8-hour oral mucosal microcirculation.

Research Design

This study was a prospective, observational and descriptive, repeated measures design that compared the measurements of microcirculation variables of orally intubated patients using the AnchorFast securement of the ETT.

Population and Participants

Nine patients were recruited from a population of adult intubated patients at QMC MICU between January 7, 2016 to June 30, 2016. The sample were those patients admitted to the QMC MICU cared for by the MICU team care service. A convenience sample was used because of limited rental agreement period of CytoCam.

Inclusion and exclusion criteria.

- *Inclusion Criteria.* Patients were eligible to participate in the study if they (or the legal authorized healthcare decision maker): 1) Were admitted or transferred to the QMC MICU between 4am to 3pm and were intubated less than 4 hours; 2) Were age 18 years old or greater; 3) Was able to be in a supine position with the head of the bed elevated at 30 degrees; 4) Was able to use the AnchorFast for ETT securement; 5) Could give informed consent (or

the legal authorized healthcare decision maker); 6) Were not required to have medicated ointment applied to their upper lip; 7) [the patient's representative] was fluent in English; 8) Anticipated to be intubated longer than 12 hours; and 9) received the MICU standard of care for ETT management (see Appendix C) and the QMC Ventilator Associated Pneumonia (VAP) / Ventilator Associated Event (VAE) bundle.

- *Exclusion Criteria.* Patients were excluded from participation if they: 1) Were admitted or transferred to the QMC MICU between 3:01pm to 3:59am and intubated greater than 4 hours prior to QMC MICU; 2) Had a surgical intervention to the oral area such that RCP could not follow the QMC guideline for AnchorFast; 3) Had pressure ulcers, any wound, or trauma to upper lip prior to/upon admission; 4) Were required to have medicated ointment applied to their upper lip; 5) Were allergic to the water soluble lip moisturizer used by the MICU; 6) Required a bite block; 7) Was unable to give informed consent or had a legal authorized healthcare decision maker who would not provide informed consent; 8) [the patient's representative] was not fluent in English; 9) Was anticipated to be intubated less than 8 hours; 10) Was going to procedures within first 8 hours of admission; 11) Was sitting up in chair within first 8 hours of admission; 12) Could not routinely be turned/repositioned every 2 hours; or 13) did not receive the MICU standard of care for ETT management (see Appendix C) and the QMC Ventilator Associated Pneumonia (VAP) / Ventilator Associated Event (VAE) bundle.

Research Site

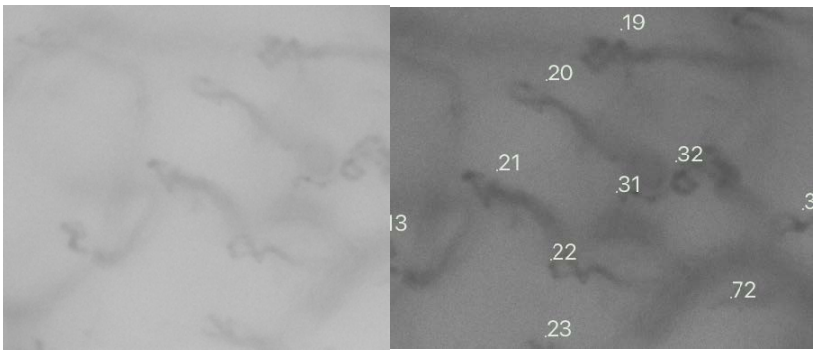
This study took place at the QMC (Punchbowl) MICU, Honolulu, Hawai`i. This institution is a private, nonprofit, acute tertiary care facility with 535 acute and 40 sub-acute licensed beds. The MICU is an all-private room 19-bed unit with designated airborne isolation rooms, hemodialysis rooms, and an obstetrics and gynecology room. The unit operates on a 24-hour basis with 24-hour intensivist coverage. At the time this study took place, the average daily census was 14.8 patients. During the study period, the 19-bed MICU had an average 78% occupancy rate with an average 45 intubated patients per month and an average length of stay of 4.14 days. The MICU provides care for adults and adolescents over age 15. The most frequent diagnoses included patients presenting with status post 'Code Blue', respiratory failure, gastro-intestinal bleeding, diabetic emergencies, acute renal failure, sepsis/multi-system organ failure, and drug overdose.

As part of its day-to-day operations, the MICU also provides care to overflow surgical, neurosurgical, and cardiac ICU patients, as well as telemetry patients. It should be noted that all patients admitted to the QMC MICU must meet admission criteria per the QMC Critical Care Protocol and will have a point physician intensivist who has responsibility for coordinating and communicating the overall care of the patient. Upon admission, an MICU registered nurse (RN) initiates the nursing process for assessment, data collection, and care planning which includes the patient, his/her family and/or significant other in education needs, discharge planning needs, and ongoing clinical care.

Operational Definitions

- *Microcirculation* is defined as passage of blood in the smallest vessels, namely arterioles, capillaries, and venules ("microcirculation", 2012). The CytoCam (see Appendix A) was used in this study to measure microcirculation of the inner aspects of upper lip mucosa and is described in terms of following variables:
- *Total Capillary Density (TCD; capillaries per millimeter squared [cpll/mm²])* is defined as the total number of all capillary loops present (regardless of its functional state) per visual field (Milstein et al., 2012) (see Figure 2). For the purposes of this study, this parameter was derived directly from three adjacent imaged clips from the designated region of interest (ROI), a mean from those three clips was used to represent the TCD of the targeted tissue site. The TCD count was taken on a frame size of 1.8 mm². The data for his parameter was quantified offline from the recorded files using Adobe Photoshop counting tool function.

Figure 2. Lip mucosa TCD processing derived from CytoCam system



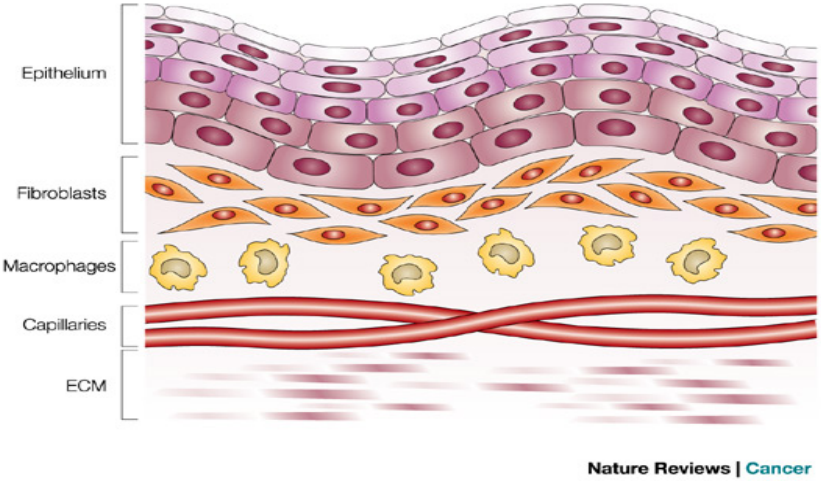
- *Functional Capillary Density (FDC; capillaries per millimeter squared [cpll/mm²])* is defined as the total number of functional

capillary loops present per visual field (Nolte et al., 1995; Milstein et al., 2012). Diffusion- and convection-based parameters are two main principles that describe how oxygen and blood reach the tissues from the microcirculation and define the main microcirculatory functional parameters obtained from microcirculatory images (Medina, Milstein & Ince, 2014). The FCD count was taken on a frame size of 1.8 mm².

- *Microcirculatory Flow Index (MFI; arbitrary units [AU]).* This is the overall score computed for each selected vessel as described by Boerma et al. (Boerma et al., 2005). This is based on determination of the predominant flow type in each video sample using an ordinal scale consisting of either a score of 0 (no flow), 1 (intermittent flow), 2 (sluggish flow), or 3 (continuous flow) in each of the four quadrants in the field of view of each imaged sample. The MFI was assessed on a frame size of 1.8 mm².
- *Proportion of Perfused Capillaries (PPC; percentage [%]).* This parameter is computed as a percentage and used to describe a ratio between perfused and non-perfused capillary loops in the ROI. Essentially this defines the amount of non-perfused versus the perfused capillary densities in the tissue of interest and can provide a way to quantitatively and describe mucosal perfusion level.
- *Blood Vessel Diameter (BVd; micrometer [µ])* is a parameter only available using the current gold standard software, AVA v3.02 (MicroVision Medical BV, Amsterdam, The Netherlands). It requires selection of 20 vessels (at random) (Tytgat et al., 2013; Dirkes et al., 2015) or more capillary loops to describe the potential changing morphologies of the capillary calibers in response to a stimulus (i.e. in this case ischemia from positioning of the ETT).
- *Oral mucosa* is defined as the mucous membrane lining the cavity of the mouth, including the gums (“Oral mucosa”, 2012). It is “comprised of stratified squamous epithelium that overlies the lamina propria, which consists of fibroblasts and connective tissue, small blood vessels (capillaries), inflammatory cells (macrophages), and extracellular

matrix (ECM)" (Sonis, 2004) (see Figure 3). The upper lip mucosa in this study is the inner aspect of the lips and is not keratinized.

Figure 3. Oral Mucosa [from Sonis, 2004]



- *ETT pressure* is defined as pressure on the upper lip mucosa against ETT while patient is intubated.
- *ETT reposition* is defined as repositioning the ETT while it is secured with AnchorFast Oral ETT Fastener (see Figure 4). A special feature on AnchorFast allows changing the ETT position from side to side along the tube track.

Figure 4. AnchorFast oral endotracheal tube fastener

Research Question 2. What relationships exist between participants' age, vital signs (including body temperature, heart rate (HR), mean arterial pressure (MAP), Sequential Organ Failure Assessment (SOFA) score, and Braden Scale score and oral mucosal microcirculation.

Definitions.

- *AnchorFast* is a device to secure oral ETT and is manufactured by the Hollister Technology (see Appendix B).
- *SOFA score* is defined as a mortality prediction score that is based on the degree of dysfunction of six organ systems (Kamal, 2015). The tool tracks a patient's status during their ICU stay. The score is composed of sub-scores from 6 systems of the body (respiratory, cardiovascular, hepatic, coagulatory, renal, and neurological). Each system is graded from 0 to 4 points according to the degree of dysfunction: The higher the score, the higher the dysfunction (see Appendix 4). The assignment of a score for each system is based on one or more variables. The SOFA score is a reliable outcome predictor (Ferreira, Bota, Bross, Melot, & Vincent, 2001), and the Primary Investigator (PI) has been trained to calculate the scoring for this study. SOFA score at the time of admission was used. Every third calculation was validated with the MICU intensivists.
- *BSPPSR - Braden Scale for Predicting Pressure Sore Risk* is defined as a pressure ulcer development risk prediction score that is based on a patient's sensory perception, skin moisture levels, activity, mobility, nutrition, friction, and shearing (see Appendix F). Scores range from 6 to 23. A score of 15-18 indicates that the patient is at mild risk for developing a pressure ulcer; a score of 13-14 indicates moderate risk; a score of 10-12 indicates high risk; and a score of equal to or less than 9 indicates severe risk (Braden & Bergstrom, 1988). Braden Scale score at the time of admission to MICU was used for this study.

Sampling

Recruitment plan

Once the admitting MICU intensivist notified the charge RN of a potential admitted or transferred patient, the charge RN notified the Principal Investigator (PI) or the research

assistant RN for possible participant recruitment. The PI or research assistant RN obtained informed consent from the eligible participants or their designated decision maker/guardian.

Power Analysis. The number of eligible participants that were enrolled and completed the study during the enrollment and data collection period determined the sample size (n=6). For this analysis, if the variance was small and the effect size was 'medium' (0.3), then for power of 0.9, the researched needed at least 22. If the variance was large and the effect size was kept to medium, then the researcher needed sample size of 39 for power 0f 0.8. The medium sample size was 'conservative' from the book based on non-repeated measures. Therefore, depending on the effect size, the minimum sample size would be 20 which would get the researcher at least power of 0.8 or more for a medium effect size and alpha=.05.

Measures

The participant's medical record number (MRN) and intubation date and time was collected from the EMR. This study utilized 9 instruments to collect the following data: Age, body temperature (T), heart rate (HR), blood pressure (systolic, diastolic and mean arterial), SOFA score, Braden Scale score, TCD, FCD, PPC, MFI and BVd. Participant age was age on admission to QMC. ICU routine vital signs (T, HR, BP) were taken hourly unless hemodynamically unstable.

*SOFA score***.** The SOFA instrument tracks a patient's status during the stay in an ICU. The scoring system determines the extent of a person's organ function or rate of failure. The score is composed of individual scores from six systems of the body (respiratory, cardiovascular, hepatic, coagulation, renal & neurological). Each of the 6 systems were graded from 0 to 4 points according to the degree of dysfunction; the higher the score, the higher the degree of dysfunction. The reliability and accuracy of SOFA scoring are considered "good" (Arts, Keizer, Vroom, & de Jonge, 2005), and several studies indicate that it is a useful predictor of patient outcome in critically ill patients (Ferreira, Bota, Bross, Melot, & Vincent, 2001; Vincent et al., 1998; Zygun, Berthiaume, Laupland, Kortbeek, & Doig, 2006).

BSPPSR. The Braden Scale score includes 6 risk factors: sensory perception, moisture, activity, mobility, nutrition, and friction and shear. Each factor is measured with a point scale, where a score of 1 means a high risk and 3 or 4 a low risk (Halfens & Van Achterber, 2000). At QMC, the total Braden Scale score of nine or below is very high risk, 10-12 is high risk, 13-14 is moderate risk, 15-17 is low risk, and 18 or more is no risk. More than 11 published studies report the reliability of Braden Scale with inter-rater reliability

ranging from 0.83 to 0.99, with percent agreement ranging from 88% to 100% (Kring, 2007). The validity of the Braden Scale has sensitivity ranging from 61% to 100% at optimal Braden Scale cut-off points and specificity ranging 26% to 100% at optimal Braden Scale cut-off points; variations are based on the care setting and patient population (Kring, 2007).

*Microcirculation variables***.** Microcirculation variables such as TCD, FCD, PPC, MFI and BVd were measured using the CytoCam. This device is a non-invasive, incident dark-field imaging (IDF) based (Sherman et al., 1971; Slaaf et al., 1987) handheld microscope ("CytoCam", 2015). The device is a lightweight pen-like instrument with a length of 220 mm and diameter of 23 mm. It consists of a probe that incorporates stroboscopic green LED light (540 nm) illumination resulting in IDF illumination with a field of view of 1.55 x 1.16 mm (Aykut et al., 2015). "Combined with a set of high resolution lenses (magnification x4), it projects images onto a high-resolution computer-controlled image sensor" ("How it works/CytoCam-IDF", 2015). The camera is connected to a medical grade panel PC, where the recorded images and analyses are stored. All data collected with the CytoCam conformed to the recommendations outlined by international consensus on microcirculation data acquisition and analysis (De Backer et al., 2007). The obtained parameters provide the following information: 1) How many capillaries are perfused, 2) What is the quality of the flow, and 3) Are there non-perfused areas next to well-perfused areas (Milstein et al., 2012; Weber et al., 2014; Aykut et al., 2014).

Procedures

Data Collection

The study was conducted on patients admitted to QMC's MICU who met inclusion criteria. Data was collected for 6 months (from January 7, 2016 to June 30, 2016). Upon receiving Institutional Review Board (IRB) approval, the MICU staff was oriented to the study. All patients received the MICU standard of care for ETT management (see Appendix C) and the QMC Ventilator Associated Pneumonia (VAP) / Ventilator Associated Event (VAE) bundle which included: 1) Elevating head of bed (HOB) ≥ 30 degrees, 2) Usage of Hi-Lo Subglottic aspiration ETT, 3) Use of separate suction canisters for oral and endotracheal secretions, and 4) Providing oral care every 4 hours.

After obtaining informed consent, data was collected from the participants' EMR, including body temperature (T), mean arterial pressure (MAP), Braden Scale score, Sequential Organ Failure Assessment (SOFA) score, intubation date and time, and ETT repositioning date and time. Microcirculation variables such as TCD, FCD, PPC, MFI, and BVd were measured using the CytoCam. During microcirculation data collection, all

participants were in a supine position with HOB elevated for 15 minutes at a minimum of 30°, with the ETT secured to the upper lip which is standard practice in the MICU. In the MICU, ETT are routinely maintained in a 'neutral position' as standard practice. An arm extends from the ventilator to hold the circuit that attaches to the ETT in such a way to prevent tugging action against to labial area. If additional support is required, a rolled towel is normally placed under the ETT to main a neutral position. Microcirculation of the oral mucosa was measured using the CytoCam Video Microscope System (Braedius Medical, Huizen, The Netherlands). CytoCam images were used to collect both diffusion-related parameters (i.e. microvascular density such as TCD, FCD, and PPC; parameter indicative for oxygen distribution) and convection-related parameters (i.e. microvascular flow properties such as MFI and BVd) in accordance with international consensus on microcirculation data acquisition and analysis recommendations (De Backer et al., 2007). It should be noted the time for repositioning of ETT in order to collect microcirculation data with the CytoCam was estimated to take approximately 11 seconds. This includes approximately 1.25 ± .02 seconds for repositioning of the ETT (Fisher, Chenelle, Marchese, Kratohvil, and Kacmarek, 2014), plus 5 seconds to position the CytoCam probe on the region of interest (ROI), followed by an immediate capture of the video image which took 4 seconds. The process was repeated 2 additional times, adding 8 seconds, for a total capture of 3 videos. The total time to collect microcirculation data was estimated to take 11 seconds plus 8 seconds, or a total of 19 seconds. If the participant's head or mouth moved during this process, additional time must be taken into account and detailed description of additional time usage should be recorded for possible variabilities.

Frequency of data collection. Data was collected from participants during the first 8 hours from admitting in MICU. T, HR, SBP, DBP, MAP, and OM microcirculation variables (TCD, FCD, PPC, BVd, and MFI) were collected every 2 hours (Table 2; Appendix E).

Management of collected data. All consents and data were stored in a locked research cabinet, and the CytoCam was locked in MICU nurse manager's office when not in use. Only the PI, research assistant nurse and Dr. Scott Gallacher had access to the research data and the CytoCam. Off line data was available to Dr. Dan Milstein for verification.

Measurements of Microcirculation of Upper Lip Oral Mucosa

Locations of microcirculation of upper lip oral mucosa measurements are described in Figure 5. Microcirculation variables were measured in Area 1. Steady images of 4 seconds were acquired and stored. At each measurement point, the vital signs were collected. Microcirculation were measured as follows:

1. Measured Area 1's TCD, FCD, PPC, MFI, and BVd as a baseline value (all data analysis was processed after acquisition). A straight line up from this area was marked on the AnchorFast track area with a blue marker and was named Area 1. Area 1 and Area 2 were arbitrary locations to explain protocol procedures. Area 1 was identified as the lip area where no contact of ETT from initial intubation and Area 2 was identified as the lip area where ETT contacts upon initial intubation.
2. Once obtaining Area 1's baseline values of TCD, FDC, PPC, MFI and BVd, the ETT was placed on Area 1 for 2 hours (see Figure 3). The PI recorded the time of ETT repositioning.
3. The PI checked the time of intubation in the participants' EMR. Initial ETT interface area was named Area 2.
4. After 2 hours from initial repositioning of the ETT (Area 2 to Area 1), the PI and Respiratory Care Practitioner (RCP) repositioned the ETT to Area 2.
5. The PI measured Area 1'sTCD, FCD, PPC, MFI, and BVd immediately (within 2 minutes).
6. After measuring Area 1 at 2 hours, the PI and RCP repositioned the ETT back to Area 1. The ETT remained at Area 1 for another 2 hours.
7. After 2 hours from step 6, the PI and RCP repositioned the ETT to Area 2. The PI measured Area 1's TCD, FCD, PPC, MFI, and BVd immediately (within 2 min) after re-positioning the ETT to Area 2. Area 3 was considered the ETT free area during measurement of Area 1 and 2's microcirculation variables.
8. After measuring Area 1 at the 4-hour mark, the ETT was repositioned back to Area 2 and remained in Area 2. This complies with current QMC AnchorFast guideline that the ETT is repositioned after 4 hours in one place.
9. After 2 hours from no contact of the ETT in Area 1, the PI measured Area 1's TCD, FCD, PPC, MFI, and BVd. This step was to assess if Area 1 had possible reperfusion ischemia or injury 2 hours free of the ETT contact.
10. After 4 hours from no contact of the ETT in Area 1, the PI measured Area 1's TCD, FCD, PPC, MFI, and BVd. This step was to assess if Area 1 had possible reperfusion ischemia or injury 4 hours free of the ETT contact.
11. The PI and nursing staff continued care using the current QMC AnchorFast guideline.

Figure 5. Locations of microcirculation measurements

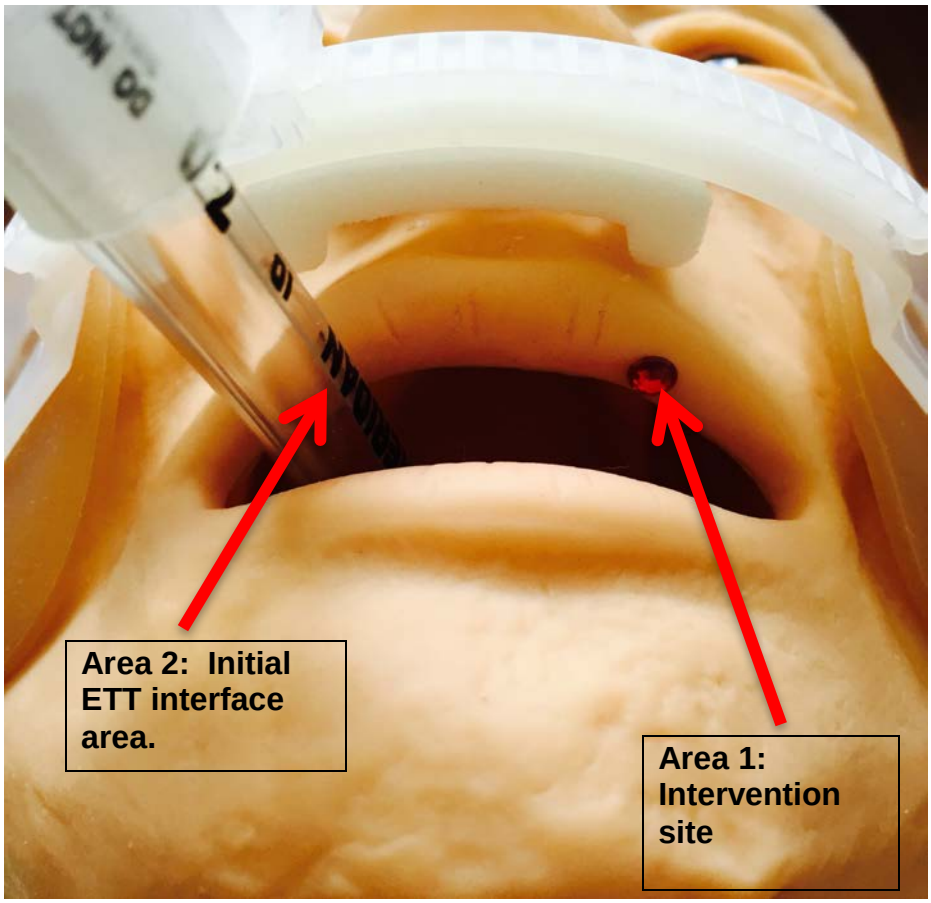


Table 2. Summary of data collection procedure

Data Collection Time	Location of Measurement	ETT Location during Data Collection	ETT Location immediately after Data Collection	CC Variables	EMR Variables
Upon recruitment	Area 1	Area 2	Area 1	TCD, FCD, PPC, MFI, BVd	T, HR, SBP, DBP, MAP, SOFA score, Braden Scale score
After obtaining baseline measurements of Area 1, repositioned the ETT from Area 2 to Area 1.					
2-hours after reposition	Area 1	Area 2	Area 1	TCD, FCD, PPC, MFI, BVd	T, HR, SBP, DBP, MAP
4-hours after reposition	Area 1	Area 2	Area 2	TCD, FCD, PPC, MFI, BVd	T, HR, SBP, DBP, MAP
2-hours after reposition	Area 1	Area 2	Area 2	TCD, FCD, PPC, MFI, BVd	T, HR, SBP, DBP, MAP
4-hours after reposition	Area 1	Area 2	Area 2	TCD, FCD, PPC, MFI, BVd	T, HR, SBP, DBP, MAP

Assurances of Interrater Reliability

The intraclass correlation coefficient (ICC) was used for the analysis of the interrater reliability test. A high degree of reliability was found between PI's and expert's TCD measurements. The single measure ICC was .974 with a 95% confidence interval from .826 to .996 ($F(5,5) = 74.771$, $p=.000$). A high degree of reliability was found between PI's and expert's FCD measurements. The single measure ICC was .970 with a 95% confidence interval from .801 to .996 ($F(5,5) = 64.807$, $p=.000$).

Data Management

To prevent inadvertent re-enrollment, the enrolled patient's name and medical record number (MRN) were recorded on a paper data record book during recruitment and stored in the binder. Data was entered into and stored on the researcher's personal, password-protected computer with only the assigned numeric codes to de-identify data and enhance confidentiality. The binder, along with all participant data was collected and saved on a USB flash drive (Kingston Data Traveler Locker+G2) that has built-in encrypted capability and

was stored in a locked file cabinet in the MICU nurse manager's office. The PI did not save any data on the hard drive of the project's password-protected laptop.

Human subjects

Informed consent.

This proposal was submitted to the QMC IRB and the University of Hawai`i IRB. Prior to study enrollment, informed consent was obtained from each participant or their decision makers by the PI or research assistant RN at QMC.

Anonymity/confidentiality.

All personal information was de-identified before data entry. Results of this research was only presented as grouped data.

Penalty for non-participation/withdrawal or preferential treatment for participation.

Participants had the option to withdraw from the study at any time for any reason. Participants were allowed to withdraw or decline participation without any interference of care the participant received at the time of the study or in the future. There was no preferential treatment for participation.

Risks and benefits

Risks. Using non-invasive technology to measure microcirculation of upper lip oral mucosa for short period of time (4 seconds per study sites) has minimal risks to participants. Previous studies indicated was no risk or side effects using CytoCam (IDF technology).

Benefits. Findings from this study will help clinicians understand more about upper lip oral mucosa microcirculation changes in intubated patients and the benefits of repositioning of ETT to prevent ETT related OMPrUs.

Data and safety monitoring plan.

Adverse event (AE) reporting. No AE occurred. If there was an AE, the researcher was going to reported to the IRB and Medical Director of MICU, and the study halted during investigation of the event.

Risk minimization.

The risk of causing pain during data acquisition was minimized in two ways:

- During the data acquisition, patients were reassured that data acquisition was done by lightly touching the inner upper lip.
- If patients were experienced excruciating pain, the data acquisition would not continue.

Study termination, early withdrawal of individuals.

Participants had the option to withdraw from the study at any time for any reason.

Confidentiality.

All of the participants' information was de-identified before data entry.

Data Security.

Participant information/demographics was known only to the researcher. Vital signs were shared information among MICU nurses, doctors, and consultants for medical treatment and intervention. Oral mucosa microcirculation information was only shared with Dr. Milstein for expertise. Participants information was only obtained during IRB approved period.

Record retention.

The researcher will retain copies of the data in secure file for the length required by the IRB.

Chapter 3 Summary

Many patients admitted to critical care units already have compromised systemic microcirculation due to sepsis, diabetes, and cardiovascular diseases (Weber et al, 2014). Direct pressure by medical devices is known to cause mucosal pressure ulcers, and intubated patients in critical care units have additional risk to develop OMPrUs from ETT. A prospective, descriptive, repeated measures design was used to compare the measurements of microcirculation variables of orally intubated patients using the AnchorFast securement of the ETT.

Chapter 4. Statistical Analysis

Descriptive statistics, Nonparametric one-way ANOVA with repeated measures (Friedman Test) and Spearman's correlations were used. If statistically significant differences were found with the ANOVA, then pairwise multiple comparison tests were used to find where the differences occur. The level of significance was 0.05 for all analyses All statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

Sample

Two hundred intubated patients were under the care of QMC MICU at the time of data collection (January 7, 2016 to June 30, 2016). 72 patients out of 200 patients were admitted between 4am and 3pm. Ten patients were eligible for recruitment. Of those 10 patients, 1 patient declined to participate in the study. Nine patients provided consent, 1 patient's condition became severely deteriorated within 2 hours of recruitment and was not able to obtain data longer. Additional 2 participants' data was omitted from data analysis: 1 patient was coughing constantly during data collection and was not able to assess accurate capillary counts and flow upon completion of all data collection; 1 patient's video clip background was too bright to assess measurements. Analysis herein is based upon the remaining 6 participants. Data were collected on QMC MICU only.

Participants' Demographic and Clinical Characteristics

The mean age of participants was 54 years old (range 32-71) (±14 SD), the mean HR was 95 (±20 SD) beats per minutes (bpm), the mean SBP was 96 bpm (±16 SD), the mean DBP was 64 bpm (±6 SD), the mean SOFA score was 12 (±2 SD) and the mean Braden Scale score was 14 (±2 SD). Three out of six participants (50%) were on anticoagulant (Enoxaparin sodium) and vasopressor (Norepinephrine).

Table 3. Demographic and clinical characteristics (N=6)

Variable	N	Lower Quartile	Median	Upper Quartile	Mean	± SD
ETT size	6	8.00	8.00	8.00	8.00	0
Age (years)	6	44.00	56.50	64.00	54.00	14.32
HR (bpm)	6	81.00	96.50	100.00	95.00	19.69
SBP (mmHg)	6	85.00	96.50	109.00	95.67	16.22
DBP (mmHg)	6	61.00	65.00	66.00	64.33	5.65
SOFA score	6	10.00	13.00	14.00	12.17	2.23
Braden Scale score	6	13.00	13.50	14.00	13.50	2.26

The mean body temperature of participants at baseline was 36.8 ℃ (±0.8 SD), 37.4℃ (±0.8 SD), 37.5℃ (±0.3 SD), 37.6℃ (±0.5 SD), and 37.7℃ (±0.9 SD) over the 8 hours

period. The mean heart rate of participants at the baseline was 95 bpm (±20 SD), 89 bpm (±13 SD), 89 bpm (±14 SD), 88 bpm (±16 SD), and 92 bpm (±15 SD) over the 8-hour period. The mean MAP of participants at the baseline was 75 mmHg (±7 SD), 77mmHg (±8 SD), 80 mmHg (±15 SD), 79 mmHg (±4 SD), and 77 mmHg (±7 SD) over the 8-hour period. The mean SBP/DBP at the baseline was 96/64 mmHg (±16/6 SD), 105/65 mmHg (±15/7 SD), 109/67 mmHg (±11/19 SD), 104/67 mmHg (±15/10 SD), and 104/65 mmHg (±16/8 SD) over the 8-hour period.

Table 4. Temperature, heart rate (HR), mean arterial pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP)

Variable	N	Median	Mean	± SD
Baseline T (℃)	6	37.00	36.82	0.79
+2 hour T	6	37.55	37.43	0.80
+4 hour T	5	37.50	37.50	0.33
+6 hour T	3	37.80	37.57	0.49
+8 hour T	5	37.40	37.74	0.89
Baseline HR (bpm)	6	96.50	95.00	19.69
+2 hour HR	6	91.00	88.83	13.23
+4 hour HR	5	95.00	88.60	14.29
+6 hour HR	4	87.00	87.75	15.54
+8 hour HR	6	93.50	91.67	14.26
Baseline MAP	6	74.00	74.83	6.91
(mmHg)	6	75.50	77.00	7.54
+2 hour MAP	5	75.00	79.60	15.34
+4 hour MAP	4	80.00	78.50	3.79
+6 hour MAP	6	76.50	76.83	7.14
+8 hour MAP	6	96.50	95.67	16.23

Research Question 1.

What microcirculation changes of upper lip oral mucosa occur from ETT pressure every 2 hours upon ETT repositioning during the first 8 hours of intubation using the ETT holder, AnchorFast? Descriptive statistics analyzed median, range, mean and standard deviation (SD) of upper inner lip mucosa (labial) microcirculation variables for 5 levels of time: baseline, 2 hours, 4 hours, 6 hours and 8 hours. Friedman's Test was used to analyze upper inner lip mucosa (labial) microcirculation variables due to very small sample size (n=6). The level of significance was 0.05.

The mean TCD at the baseline was 69.34 (±19.53 SD), 59.84 (±17.6 SD) at 2 hours, 57.34 (±18.14 SD) at 4 hours, 61.17 (± 20.92 SD) at 6 hours, and 65.34 (±21.38 SD) at 8 hours (Table 5).

Table 5. Total capillary density (TCD) *capillaries per 1.8 millimeter squared [cpll/mm²]*

Variable	N	Median	Mean	± SD
Baseline TCD	6	69.34	67.83	19.53
+2 hours TCD	6	59.84	59.22	17.6
+4 hours TCD	6	57.34	60.45	18.14
+6 hours TCD	6	61.17	58.95	20.92
+8 hours TCD	6	65.34	63.00	21.38

The mean FCD at the baseline was 65.84 (± 20.76 SD), 52.17 (±16.47 SD) at 2 hours, 49.34 (±17.42 SD) at 4 hours, 58.67 (± 20.96 SD) at 6 hours, and 60.84 (± 21.62SD) at 8 hours (Table 6).

Table 6. Functional capillary density (FCD) *capillaries per 1.8 millimeter squared [cpll/mm²]*

Variable	N	Median	Mean	± SD
Baseline FCD	6	65.84	64.78	20.76
+2 hours FCD	6	52.17	55.17	16.47
+4 hours FCD	6	49.34	55.67	17.42
+6 hours FCD	6	58.67	56.28	20.96
+8 hours FCD	6	60.84	59.39	21.62

The mean PPC at the baseline was 96.23 (±5.91 SD), 93.09 (±5.78 SD) at 2 hours, 91.83(±7.19 SD) at 4 hours, 96.46 (±4.47 SD) at 6 hours, and 93.56 (±4.74 SD) at 8 hours (Table 7).

Table 7. Proportion of perfused capillaries (PPC) %

Variable	N	Median	Mean	± SD
Baseline PPC	6	96.23	94.89	5.91
+2 hours PPC	6	93.09	93.56	5.78
+4 hours PPC	6	91.83	91.03	7.19
+6 hours PPC	6	96.46	94.77	4.47
+8 hours PPC	6	93.56	93.65	4.74

The mean MFI at the baseline was 2.84 (±0.39 SD), 2.84 (±0.39 SD) at 2 hours, 3 (±0.17 SD) at 4 hours, 3 (±0.4 SD) at 6 hours, and 3 (±0.4 SD) at 8 hours (Table 8).

Table 8. Microvascular flow index (MFI)

Variable	N	Median	Mean	± SD
Baseline MFI	6	2.84	2.72	0.39
+2 hours MFI	6	2.84	2.72	0.39
+4 hours MFI	6	3	2.89	0.17
+6 hours MFI	6	3	2.78	0.4
+8 hours MFI	6	3	2.78	0.4

Comparison of the repeated measures (oral mucosa microcirculation) was performed using Friedman's test showing a difference between baseline, 2-hour ETT position, 4-hour ETT position, 2- hour free of ETT and 4-hour free of ETT using alpha = 0.05. TCD (Friedman's Test Q = 4.13, df = 4, p=0.39), FCD (Friedman's Test Q = 4.81, df = 4, p=0.31), PPC (Friedman's Test Q = 2.32, df = 4, p=0.68) and MFI (Friedman's Test Q = 4.88, df = 4, p=0.3) were not statistically significant over all. As shown in Figures 6, 7, 8, and 9, the mean and median level of TCD, FCD, PPC, and MFI at all 5 time points (baseline, 2 hours, 4 hours, 6 hours, and 8 hours) were similar.

Figure 6. TCD mean and median over 8 hours (X mark = mean)

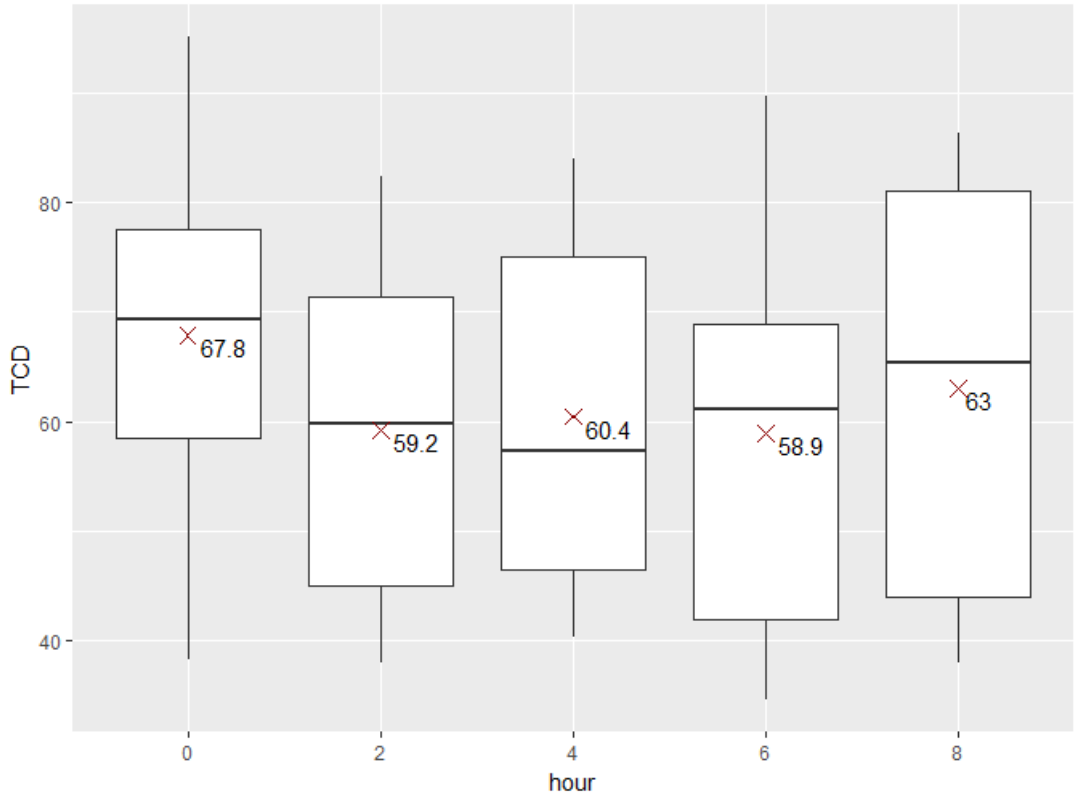


Figure 7. FCD mean and median over 8 hours (X mark = mean)

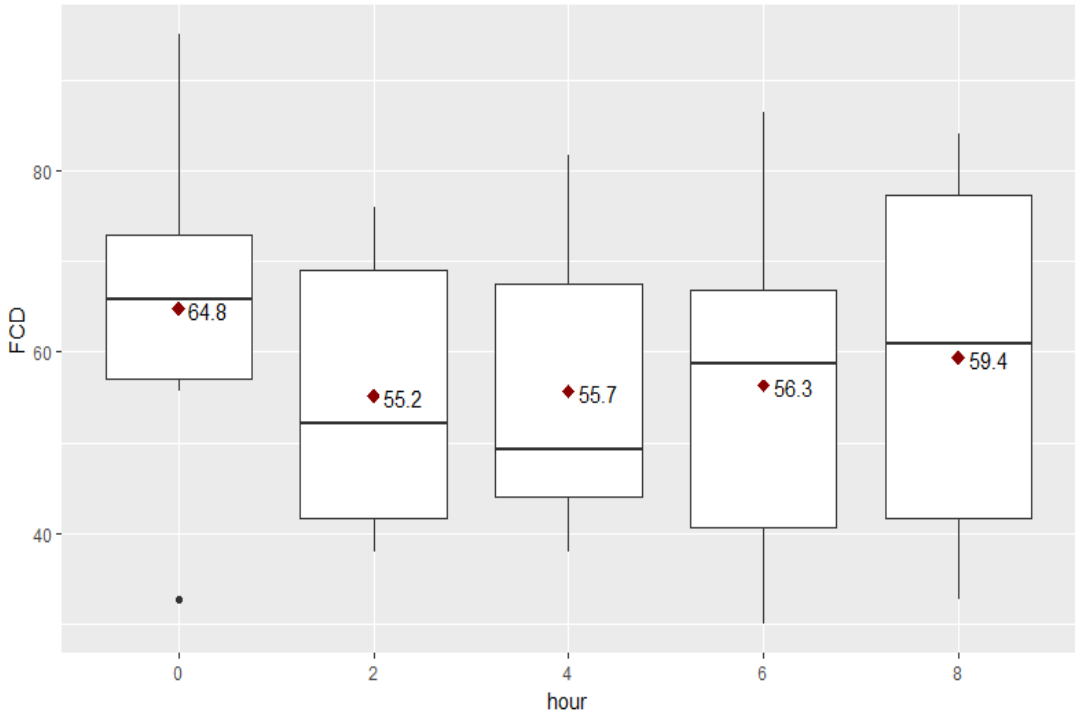


Figure 8. PPC mean and median over 8 hours (X mark = mean)

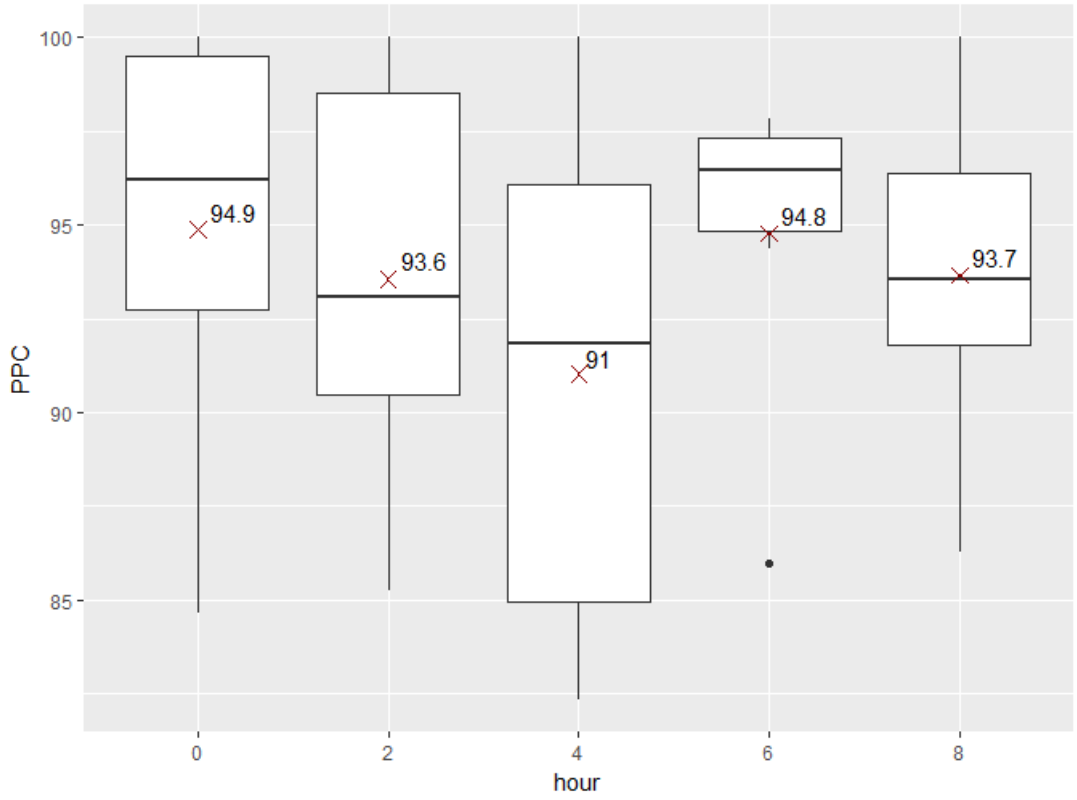
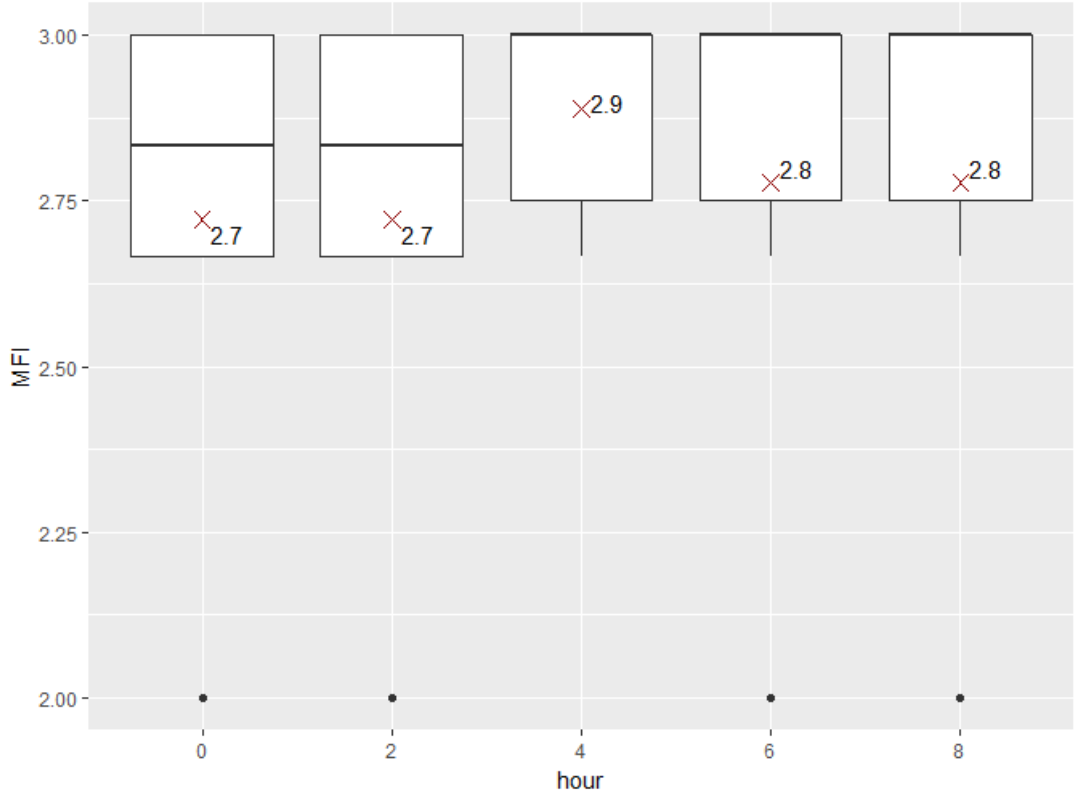


Figure 9. MFI mean and median over 8 hours (X mark = mean)



There was no significant difference of TCD, FCD, PPI, and MFI at 2-hours and 4-hours mark by Wilcoxon tests (see Figures 10, 11, 12, and 13).

Figure 10. Distribution of Wilcoxon scores for TCD

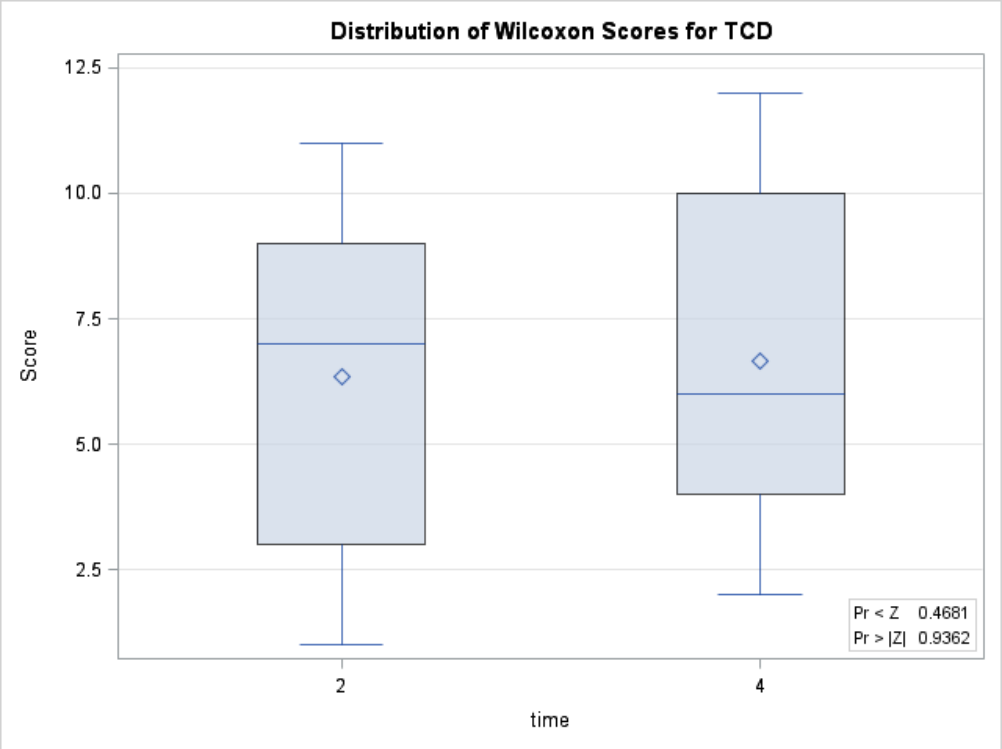


Figure 11. Distribution of Wilcoxon scores of FCD

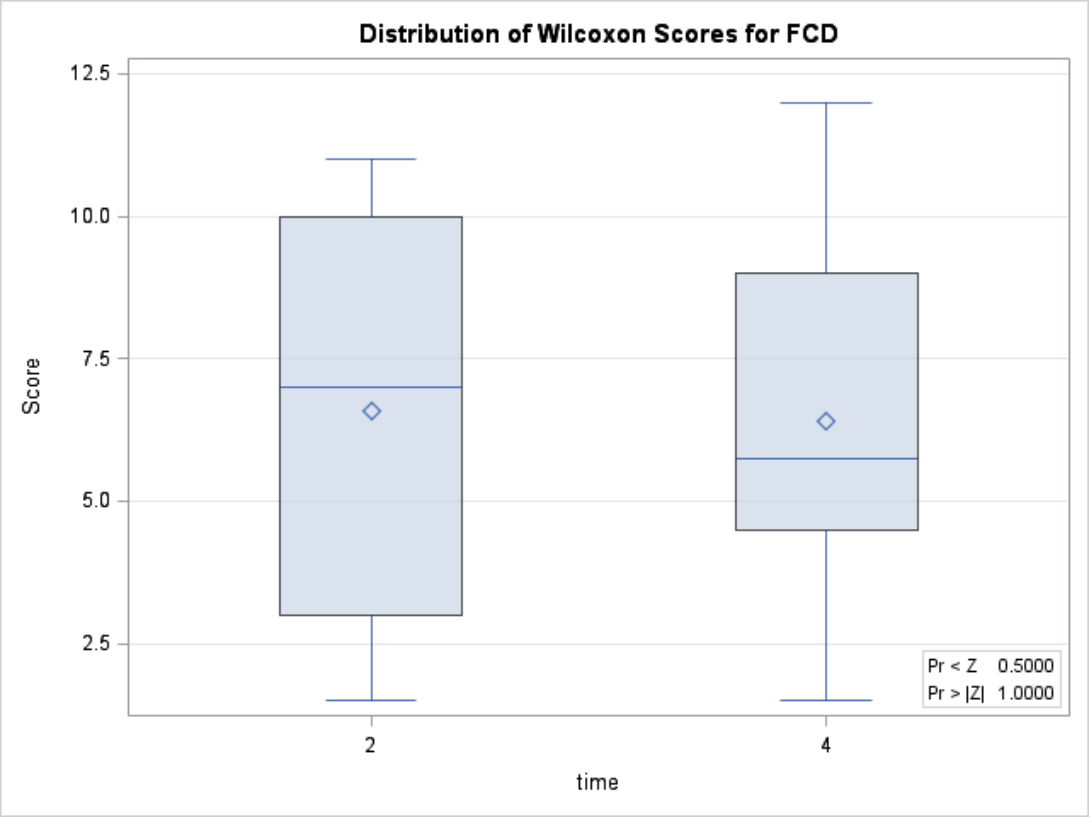
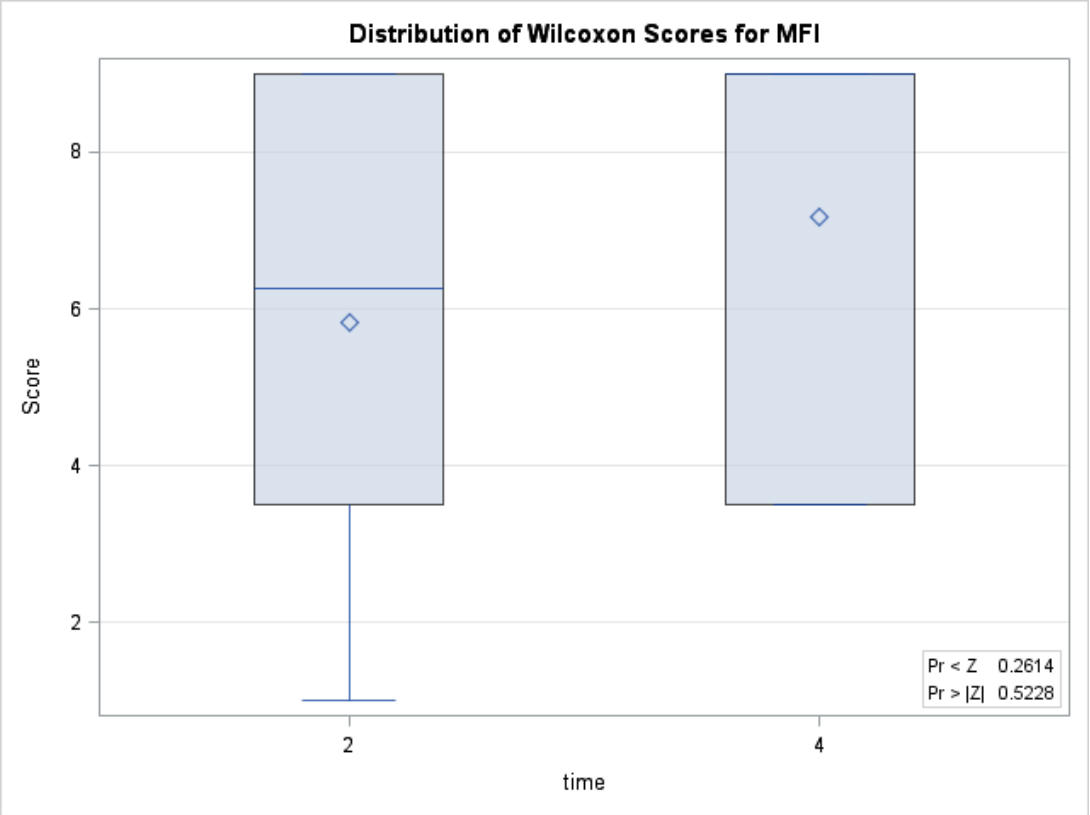


Figure 12. Distribution of Wilcoxon scores of PPI

Figure 13. Distribution of Wilcoxon scores of MFI



Summary of Research Question 1

The mean level across 5 time points had no statistically significant difference for TCD, FCD, PPC and MFI, all p>27. Comparing 2-hour and 4-hour points' TCD, FCD, PPC, and MFI reported no significant difference, p>0.57. There was high positive correlation between TCD and FCD (spearman rho > 0.9).

Research Question 2.

What relationships exist between participants' vital signs (including body temperature, heart rate (HR), mean arterial pressure (MAP)) and oral mucosal microcirculation? Descriptive statistics analyzed median, range, mean and standard deviation (SD) of vital signs for 5 levels of time: baseline, 2 hours, 4 hours, 6 hours and 8 hours. Relationships between vital signs and oral mucosal microcirculation variables were examined via the Spearman correlation coefficient. The level of significance was 0.05.

Table 8. Correlation between Vital Signs, Baseline

Mean	HR	T	MAP
FCD	-0.49	-0.81	0.37
	0.33	0.05	0.47
TCD	-0.49	-0.81	0.37
	0.33	0.05	0.47
PPC	-0.75	-0.57	0.09
	0.08	0.23	0.87
MFI	0	0.31	-0.18
	1	0.55	0.73

Table 9. Correlation between Vital Signs, at 2 hours

Mean	HR	T	MAP
FCD	-0.6	0.14	0.72
	0.21	0.78	0.10
TCD	-0.60	0.14	0.72
	0.21	0.78	0.10
PPC	0.38	-0.06	-0.43
	0.46	0.91	0.4
MFI	-0.37	0.33	0.03
	0.47	0.52	0.95

Table 10. Correlation between Vital Signs, +4 hours

Mean	HR	T	MAP
FCD	-0.66	0.82	0.83
	0.15	0.26	-0.31
TCD	-0.75	-0.17	-0.14
	0.08	0.74	0.79
PPC	0.37	0.26	-0.31
	0.46	0.61	0.54
MFI	0.31	0.1	-0.21
	0.54	0.84	0.69

Table 11. Correlation between vital signs, +6 hours

Mean	HR	T	MAP
FCD	-0.64	0.14	-0.06
	0.17	0.79	0.91
TCD	-0.64	0.14	-0.06
	0.17	0.79	0.91
PPC	-0.06	-0.25	0.32
	0.91	0.62	0.54
MFI	-0.31	0.34	-0.77
	0.55	0.51	0.07

Table 12. Correlation between Vital Signs +8 hours

Mean	HR	T	MAP
FCD	-0.37	0.37	0.31
	0.47	0.47	0.54
TCD	-0.49	0.14	0.26
	0.33	0.79	0.62
PPC	0.26	0.77	-0.14
	0.62	0.07	0.79
MFI	0.44	0.17	-0.85
	0.38	0.74	0.03

Summary of Research Question 2

Based on the results of the study, there was a statistically significant negative relationship between body temperature and TCD and FCD only, r= -0.82, p = 0.05. Also, there was a statistically significant negative relationship between MAP and MFI at 8-hour time point, r = -.85, p = 0.03. However, there was no statistically relationship between temperature, HR, MAP and TCD, FCD, PPC and MFI at 2, 4, 6-hour time points.

Research Question 3. What relationships exists between participants' age, SOFA score, and BSPS and final 8-hour time period for vital signs (including T, HR, MAP) and final 8-hour oral mucosal microcirculation? Relationships between age, SOFA score, BSPPSR, final 8-hour VS and final 8-hour oral mucosal microcirculation variables were examined via Spearman correlation coefficient. The level of significance was 0.05.

Table 13. Correlation between age, BSPPSR, and SOFA

	Age	Braden	SOFA
TCD	0.37	-0.77	0.03
	0.47	0.08	0.95
FCD	0.31	-0.85	-0.03
	0.54	0.03	0.95
PPC	0.6	-0.5	0.21
	0.21	0.31	0.69
MFI	0.44	0.68	-0.11
	0.38	0.14	0.84

Summary of Research Question 3

There was a statistically significant negative relationship between BSPPSR and TCD or FCD between subjects, $p < 0.05$. Because there were only baseline BSPPSR collected, within-subject BSPPSR association over time was not assessed.

Chapter 5. Discussion

MDRPUs are a new challenge for healthcare teams caring for critically ill patients in addition to preventing traditional pressure ulcers because medical devices are a necessity for these patients. Among MDRPUs, ETT related OMPrUs have the highest percentage of occurrence, yet there is no research specific to oral mucosa microcirculation changes related to ETT compressive force and shearing. Few studies found that using AnchorFast caused lesser OMPrUs, however the recommendation of ETT repositioning every 2 hours by the manufacture was based on patient turning schedules. Thus, it is essential to gain a better understanding of the oral mucosa microcirculation in the context of ETT related pressure ulcer prevention, and further research can help guide healthcare team members in more reliable evidence-based practices to promote safer care.

The purpose of this study was to explore the effects of ETT pressure and ETT repositioning frequency on oral mucosa microcirculation among intubated patients, it is anticipated that inspection and quantification of the oral mucosa microcirculation could guide clinicians towards the prediction and prevention of OMPrUs. Once approved by QMC's IRB and the University of Hawai`i's Human Subjects Committee, QMC MICU patients meeting the inclusion criteria were recruited and participated in the study over 6-month period. A convenience sample of data from 8 participants was completed. While maintaining patient confidentiality, the data was described, analyzed and reported in order to explore oral mucosa microcirculation related to ETT pressure and ETT repositioning frequency among intubated patients.

Interpretation of Findings

Correlation between oral microcirculation variables and compressing hours for OM by ETT

The results of 6 participants' upper lip mucosa microcirculation variables measured at 2-hour intervals (for a total of 8 hours) are presented in Tables 3, 4, 5, 6, and 7. The TCD trend minimally decreased after 2 hours of intubation and continuously decreased even after 2 hours of no ETT period. TCD increased closer to baseline after 4 hours of no ETT. The trend of FCD was more fluctuating during 8 hours of observation. The FCD trend was down the most after 2 hours of ETT compressing oral mucosa, but increased FCD trend noted 2 hours of no compressing oral mucosa (measured site after 4 hours of compressing oral mucosa and 2 hours of no compression oral mucosa). FCD decreased again even after 4 hours of no compressing oral mucosa. According to Tsai et al. (1995), "changes in FCD reflect mechanisms that modulate the entrance of red blood cells into the capillaries PPC

results were very similar pattern to FCD. These mechanisms have anatomical origin, whereby the capillary diameter changes, and may also be hydrodynamic, when flow conditions prevent red blood cells from entering a capillary branch" (p. 238). These results correlated with trend of PPC as well. The MFI remained the same overall. In theory, when no pressure exerted on the mucosa through ETT placement, MFI would climb towards normal perfusion if it indeed was compromised and scored less than 2. gradually decreased over 6 hours of intubation but improved after 4 hours of no compressing oral mucosa. Compressive force, shearing force, and patients' intrinsic variables affected oral mucosa microcirculation related to ETT.

By conducting exploratory analysis, there was high correlation between TCD and FCD illustrated by fitted non-parametric LOESS smooth curve. As shown in Figure 14, each individual's TCD and FCD association and 30 data-point TCD and FCD association had similar positive linear pattern.

Figure 14. High correlation between TCD and FCD ($r = 0.987$, $p < 0.0001$, $n=30$)

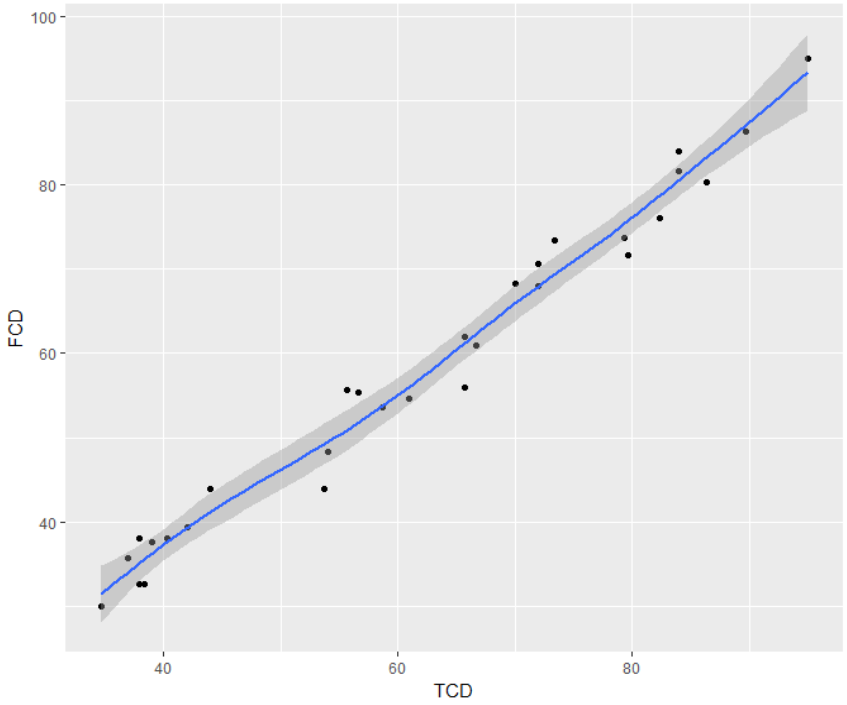
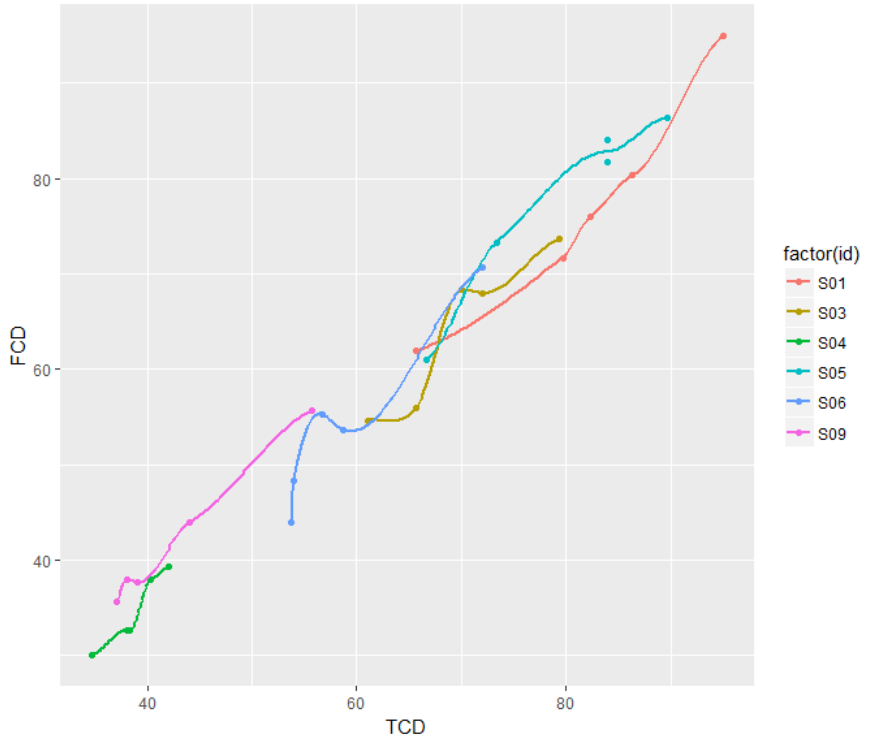


Figure 15. Participants' individual TCD and FCD correlation (r = 0.942, p = 0.0048, n=6 at end point)



Correlation between Oral Mucosal Microcirculation Variables and Vital Signs and SOFA Score

The study results showed that MFI and MAP were positively correlated and statistically significant. Improved MAP increased systemic blood flow that might affect MFI. However, the relationship between pressor (norepinephrine) and anticoagulant (enoxaparin sodium) and oral mucosa microcirculation variables was not found to be statistically significant. Studying certain regions of oral mucosa delivers vital information about particular region of oral mucosa's pathological lesions for its diagnostic purpose (Milstein, 2015, email correspondence). Need of more robust results of oral mucosa microcirculation is essential to find correlation with certain disease progress and diagnoses. There was no relationship observed between oral mucosal microcirculation variables and SOFA Score. Trzeciak et al. (2008) found that a decreased SOFA score (a lower SOFA score indicates a less patient acuity) had significant positive change in microcirculatory flow index (MFI). However, this was observed in sublingual microcirculation network, no capillary loops and not in labial mucosa. Although papillary layer capillary loops are connected to their underlying nutritive microcirculation network in the reticular layer, MFI assessment may manifest differently as advancing one level more superficially towards the sub-epithelium.

There was a trend of TCD and FCD dropped at certain temperature point (see Figures 16 & 17), HR (see Figures 18, 19), and MAP (see Figures 20,21).

Figure 16. Fitted non-parametric LOESS smooth curve of TCD and T

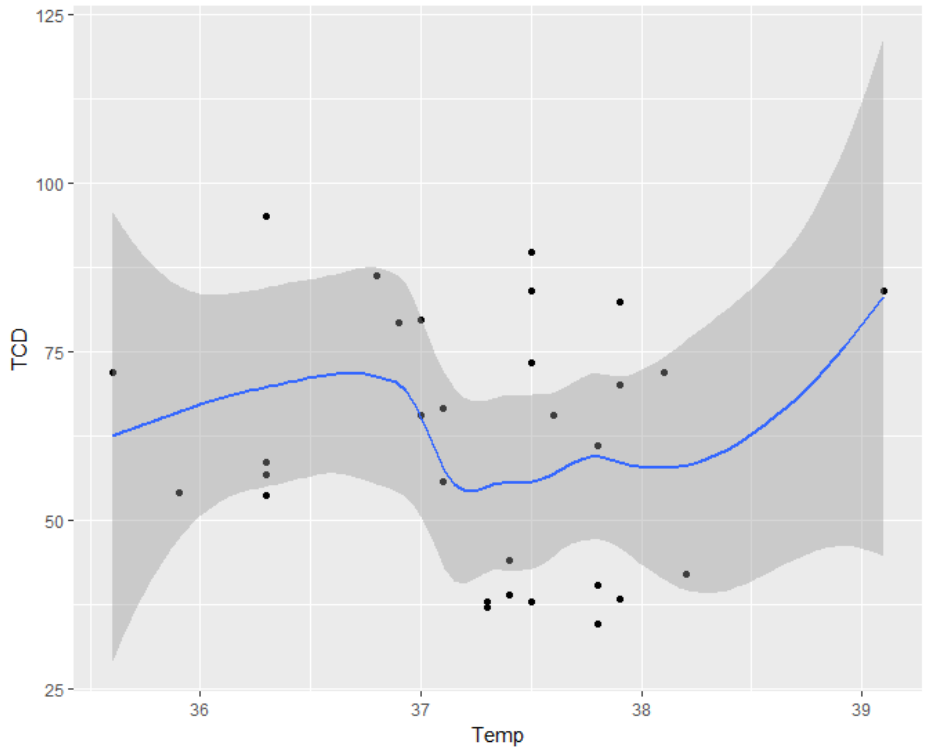


Figure 17. Fitted non-parametric LOESS smooth curve of FCD and T

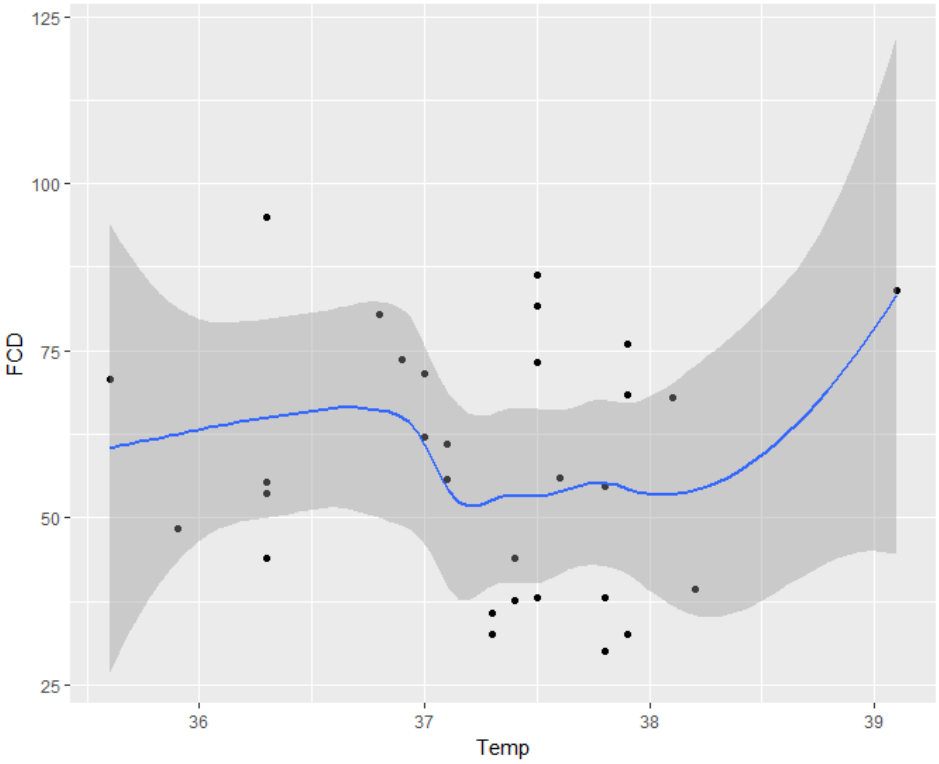


Figure 18. Fitted non-parametric LOESS smooth curve of TCD and HR

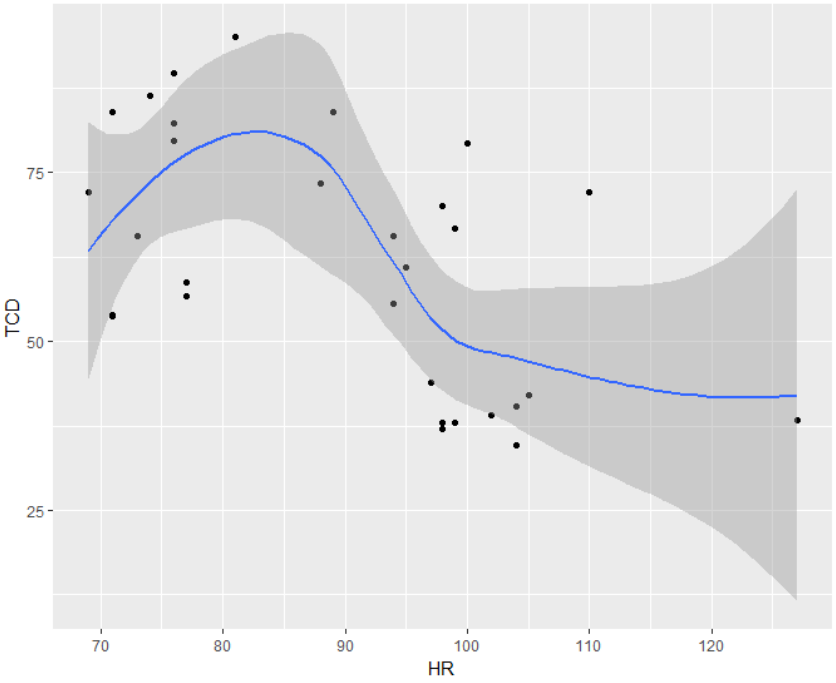


Figure 19. Fitted non-parametric LOESS smooth curve of FCD and HR

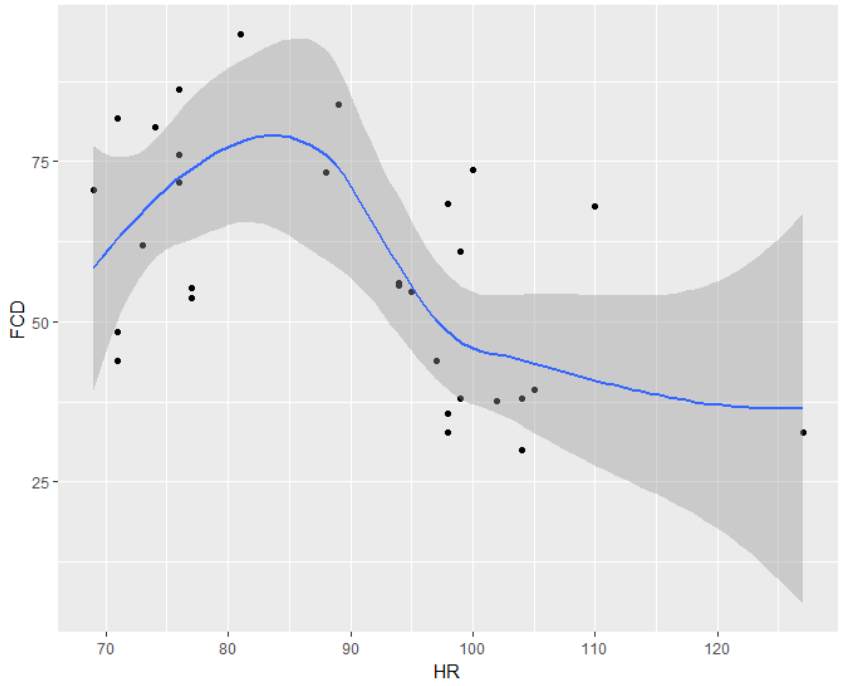


Figure 20. Fitted non-parametric LOESS smooth curve of TCD and MAP

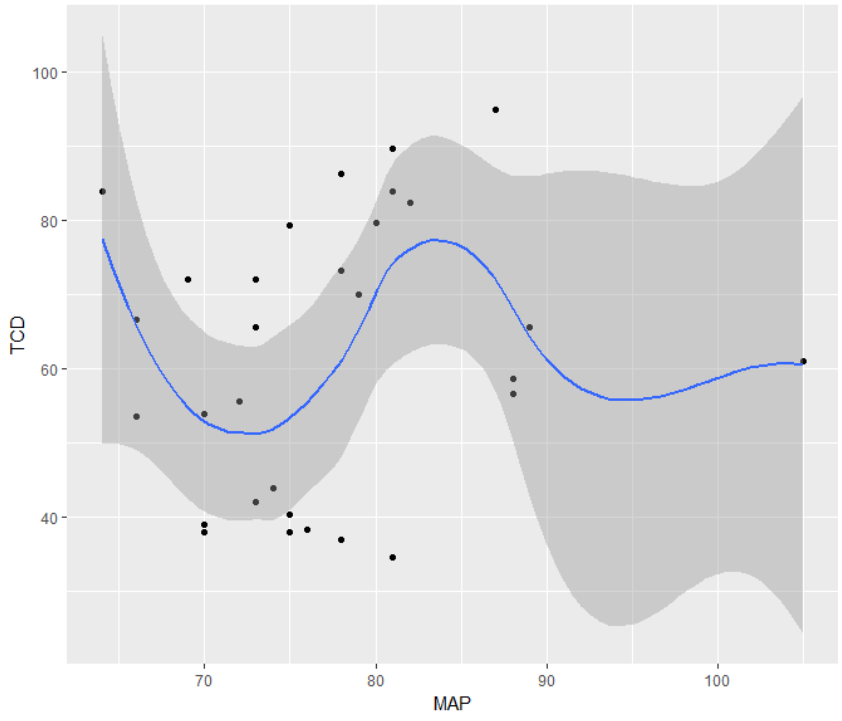
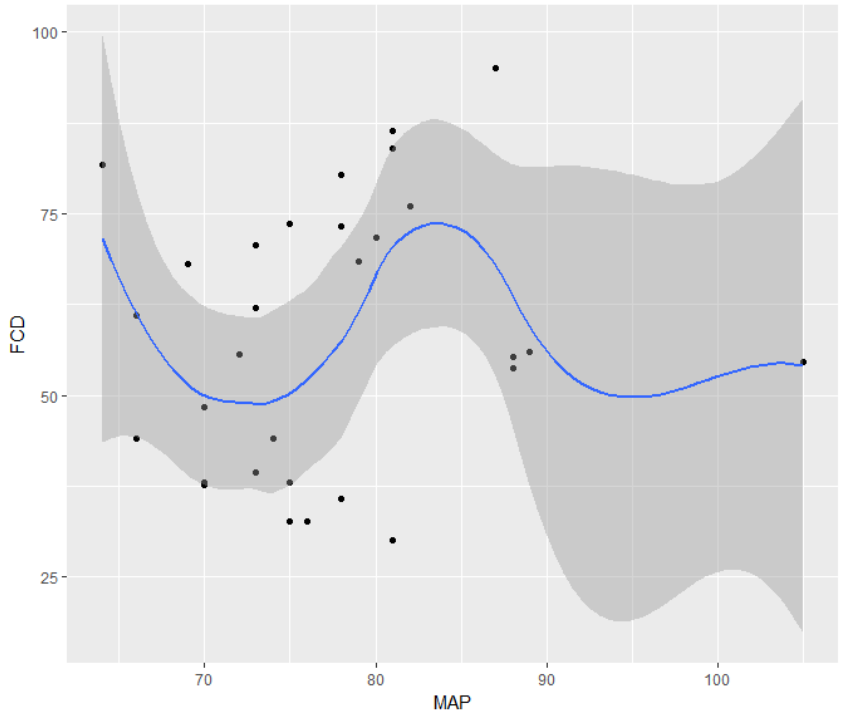


Figure 21. Fitted non-parametric LOESS smooth curve of FCD and MAP



This study did not record the presence/non-presence of a heated wire ventilator circuit which is embedded in some of the ventilators used in the MICU depending on the patient's condition. Heated wires circuit is used to ensure optimal humidification of the oxygen. It is noted that a heated wire may affect the temperature of the ROI.

Correlation between Oral Mucosal Microcirculation and BSPPSR

The baseline correlation of oral mucosal microcirculation and BSPPSR had unexpected results. Since higher the BSPPSR means healthier individuals, positive correlation was expected. However, this study results were shown negative correlation. Because this study used BSPPSR measured only at baseline, changes in the BSPPSR were not captured if the participant's condition changed over time. For example, if the participant was started on sedatives after the baseline score was assessed, the BSPPSR would not reflect potential changes in the score. In addition, the BSPPSR is designed to measure systemic issues such as sensory perception, degree to which skin is exposed to moisture, patient activity, mobility, friction and shearing, and nutrition, while this study focused on the investigation of the non-systemic local oral mucosa microcirculation. Finally, the study did not include the collection of specific sedatives given to the participants which could have affected the BSPPSR cognition subscale, which could be included in future studies. Individuals' alteration of alertness/cognition may cause higher or lower exerted pressure from individuals' behaviors such as biting ETT, moving head, trying to sit upright, trying to get out

of bed, or attempting extubation. Future research studies should include subscale of BSPPSR especially for critically ill patients.

Study Strengths

There is inadequate evidence to prevent ETT related OMPrUs. This study adds to the body of knowledge with regard to the oral mucosa microcirculation and how ETT compressive and shearing force alters oral mucosa microcirculation. Using the IDF imaging device compared to video-capillaryscopy and laser doppler, it provided better visualization of the microcirculation at capillary level.

The continuous measurement of the oral mucosa at repeated 2-hour time points up to 8 hours strengthen the study design using a participant's baseline data as control.

Study Limitations

A number of limitations must be acknowledged:

Assumptions regarding the connection between microcirculation and tortuosity of capillaries and participants' medical diagnoses were not validated in this study. Increased capillary density and tortuosity were associated in patients with diabetes according to the presence of coronary artery disease (Djaberi et al., 2012).

Isolating the pressure and shearing force of ETT that cause alteration of oral mucosa microcirculation in critically ill was not achievable. The influence of external factors on capillary recruitment was limited by standardizing the study environment such as the room temperature, degree of ETT and participants' upper lip, and room light source. Also, flow alteration in the microcirculation due to the data collector was minimized yet it can be assumed there was some pressure during acquisition of images.

The small sample size is another study limitation. Due to financial constrictions, the CytoCam was only available to the study investigators for six months. During the data collection period, an unusually lower number of intubated patients. The MICU admitted more patients on non-invasive respiratory support devices as a result of another advanced care planning project in the same MICU.

A longer training period of data collection and manipulation of the CytoCam should be considered to obtain improved image acquisition and interpretation of collected data. Understanding of flow index measurement is important that "the MFI score differentiates between the different types of continuous flows…. MFI should be preferred in more homogenous conditions because it takes into account the difference between sluggish and continuous flows" (De Backer et al., 2007).

The pressure exerted on the ROI during microcirculation data collection with the CytoCam probe was a limitation because it may cause a reactive hyperemia, or the transient increased in blood flow following brief period of ischemia.

It is difficult to apply these findings to the longer term intubated ICU patient, due to the limited 8-hour oral mucosal measurement timeframe used in this study. For example, patients who are intubated for a great time may not have the same outcome of no OMPrU found in this study sample.

This study was conducted using a convenience sample within a single ICU setting. Further restriction of data collection time occurred because of the ICU sleep program for the patients at nights.

Implications for Nursing Practice

Although endotracheal tube holders help prevent ETT related OMPrU, repositioning of ETT every 2 hours due to traditional every 2-hour turning schedule raised a question about repositioning every 2 hours would prevent OMPrU related to ETT. This study's results supported the current MICU OMPrU prevalence rate of zero for last four prevalence surveys with every 4 hours of repositioning of ETT with ETT neutral position.

Movement of evidence-based practice and research-based practice in nursing raise the bar for standards of nursing care. However, guidelines and recommendation of paucity of research studies can hinder patient safety and nursing workloads. Nurses need to make efforts to find evidences to develop standards of care and guidelines. Rigorous nursing research studies and findings make an impact to deliver safe care and break the habit of "this-is-how-we-used-to-do".

Recommendations for Future Research

Researchers have identified further systematic investigation is needed to determine how long any device can be in place before it needs to be moved or removed and how often to examine the skin (Black et al., 2010), and this study was the first step closer to researchers' recommendation. Since it was feasible to conduct this study in the MICU, it is anticipated that a larger number of participants may give us more robust results with a longer period of time especially if it was uncertain how long it would take the OM microcirculation to return to baseline values without pressure of friction and shearing for 2 hours and 4 hours.

Adequate and sufficient amount of time to train for measurements with the CytoCam is beneficial for achieving reliable and accurate data. Future study should consider more consistent environmental factors such as room temperature, room brightness, and degree of ETT to oral mucosa. Multidisciplinary research study should consider to exam other possible

variables that contribute OMPrU such as proper application of Anchor Fast, Anchor Fast with a built-in bite block, correlation with arterial blood gas and compliance of ETT neutral position. There is a need to increase the frequency and duration of the oral mucosal measurements because more data is needed to substantiate the capillary refill times due to physiological phenomenon, e.g., reactive hyperemia.

Conclusion

The assessment of oral mucosa, in this case labial mucosa, quantifying microcirculation was feasible and reproducible using the IDF imaging device for the purpose of research, yet it is noted that an adequate amount of training and understanding of interpretation of each microcirculation variable yields better experimental design and reliable scientific results. It should be noted that the procedures outlined in this research and the use of CytoCam device in an ICU's standard practice would be challenging not only because of the specialized training required to operate the CytoCam, but especially due to the specialized training needed to properly understand and interpret the measurement data.

None of the 6 participants developed OMPrU(s) from ETT and had no clinically and statistically significant changes of their microcirculation when repositioning ETT, while maintaining a neutral ETT position, every 2 hours versus every 4 hours. These research results provide a foundation of data to support such a change in future nursing practice. More research is needed to create enough evidence to support repositioning every 4 hours a standard practice in the MICU.

Appendix A

CytoCam

Braedius Medical Introduces New Cytocam

New Cytocam

The CytoCam is the latest in bedside technology to observe the human microcirculation using a handheld video microscope platform for the identification and monitoring of diseases that have potential clinical applications in the areas of Critical Care Medicine, Plastic Surgery, Wound Care and Organ Transplantation.

Unlike current instruments that were introduced in earlier years, the CytoCam sports a state of the art bedside imaging technology that combines the latest in camera and optical technology with a fan less Medical grade Panel PC Dual core processor system.

The CytoCam is very portable. Mounted on a rolling stand the instrument can be easily rolled from patient room to patient room. The small tactile probe is connected to the medical grade PC which offers a large screen for easy observation by the technician for capturing the videos.

The videos can be stored and easily analyzed on the same PC, allowing quick analysis at the bedside. New CytoCamTools V2 softwareintroducing the concept of Intervention Based Anaylsis as opposed to video based analysis, allowing to easily monitor changes of the microcirculatory parameters.

Features

- CytoCam - A Complete Solution for bed-side mircorculatory assessment
- New high speed Camera adapter developed by Braedius
- Color support and capability for realtime image processing
- a high-resolution camera,10 bit RAW, RGB
- very light and easy to handle
- high contrast images , up to 90 fps (full resolution)
- highly accurate, motor assisted focusing
- very short illumination pulse time for freezing RBC motion
- camera controller based on medical grade PC for image storage and analysis
- includes a camera adapter with a dedicated microprocessor for controlling
- extremely easy user interface. Optional: Remote control by “AirMouse”
- CytoCamTools Research Edition for camera management, capturing,
- file editing and reviewing
- CytoCamTools Optional Module for analysis of capillary density and flow

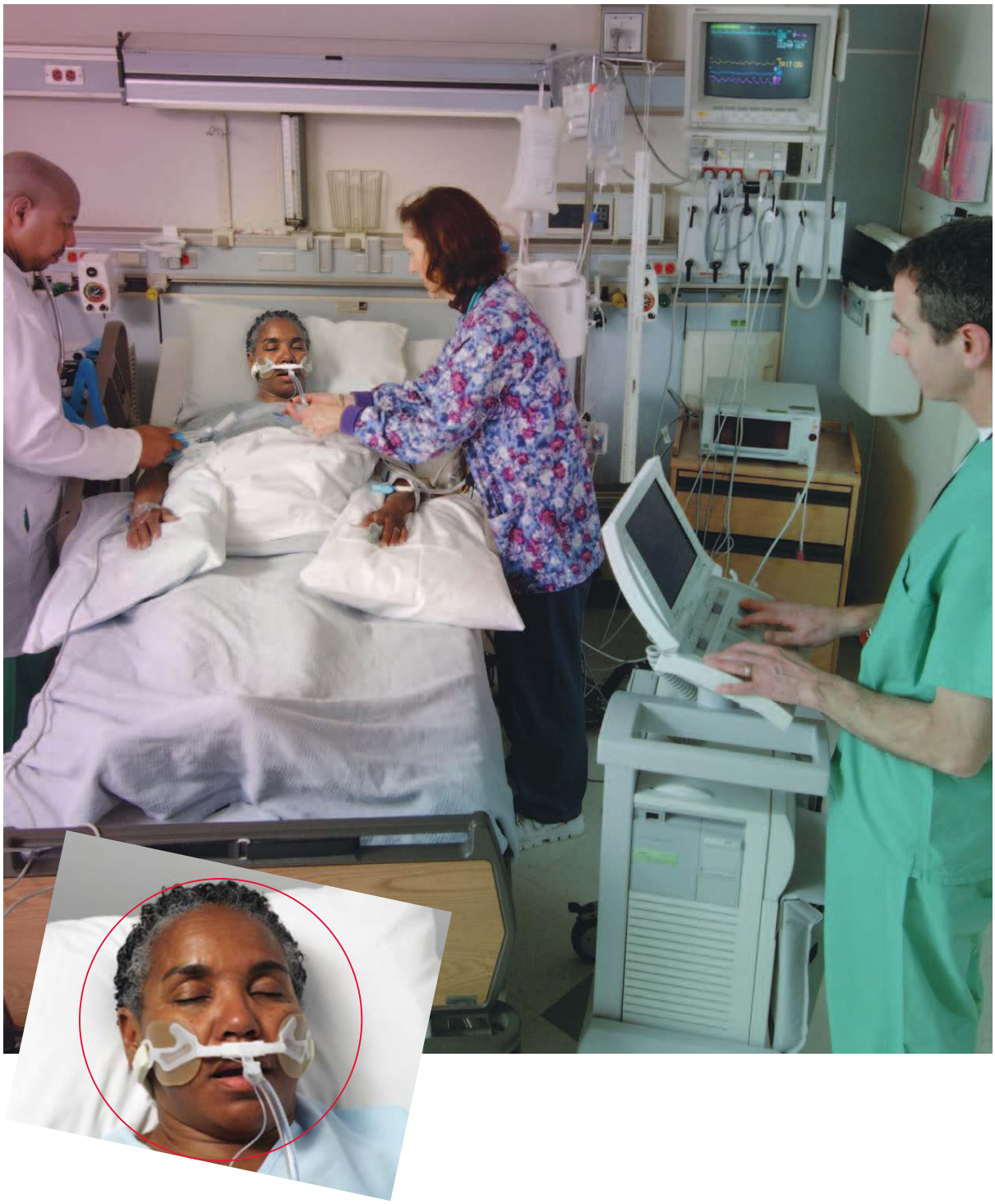
Cytocam Camera

• Sensor
  14 Megapixel: 4416 x 3312 pixels ,
  pixel size : 1,4 x 1,4 µm
  in binning mode:
  2208 x 1648 pixels, pixel size 2,8x2,8 µm
  image area: 6227x4653 µm
  output: 8 bit RAW, RGB
  image transfer rate: 25 fps (full resolution)
• Optics
  Microscopy lens designed for Braedius
  Magnification factor: 4
  Field of view: 1,55 x 1,16 mm
• Focusing
  Focusing: manually controlled motorized
  focusing system,
  Step Size 4 µm, accuracy <2 µm
• Illumination
  Based on Incident Darrkfield Imaging (IDF)
  High Brigthness LEDS

u.

Appendix B

AnchorFast



Appendix C

Guidelines for use of the AnchorFast Oral Endotracheal Tube (ET) Fastener at QMC

Guidelines for use of the Anchor Fast Oral Endotracheal Tube (ET) Fastener:
Indications for use:

• Use on patients requiring intubation for longer than 24 hours only • Use on adults with an ET tube 5-10 cm in size
• Confirm suitability:

--requires maxillary support --has intact upper teeth
--no protruding teeth
--no facial edema

• Special considerations:
--has facial hair that impedes the ability to secure the device --inability to remove facial hair
--may need to use oral airway to prevent biting down on ET

Prepare the skin and apply the fastener:

- Skin should be clean dry and free of oils ➢ Do not use skin preps

  ➢ Remove liners from the two skin barriers on device
  ➢ Center the device **gently** on the upper lip with the foam bumper touching the skin **(do not**

  apply pressure)

- Clamping mechanism should be about 1⁄2" below the lip
- Press barriers on the skin and hold in place for 30 seconds **Apply the neck band and secure the ET:**
  - Secure the neck band using the plastic loop closures. Allow two fingers width between the neck band and the neck
  - Squeeze the tabs on the shuttle, moving it over the ET tube
  - Make sure the ET tube is clean and dry
  - Remove the liner from the adhesive strap and wrap it tightly around the tube

    Secure strap by snapping the clamp shut (an audible click will be heard)

  - Document the application date or change date on Carelink (Device may remain in place for up to 7

    days)

Routine Care:

• Reposition ET tube every 4 hours or more often as condition warrants
• Assess patient's skin every 2 hours for irritation and increase frequency of repositioning if pressure

ulcer occurs
• Check and document every 2 hours to ensure that both the Anchor Fast device and the ET tube are

secure and correctly positioned.
• Under usual circumstances, replace the device every 3 to 7 days (or sooner if indicated) • Replace the neck tie when needed due to soiling

Removal

• Release the clamp
• While holding the ET tube unwrap the adhesive strap
• Release the neck band by unfastening the hook and loop closures
• Remove the skin barriers by very gently peeling away from the patient's skin to prevent injury
• Use of a warm cloth may be helpful to loosen adhesion to skin
• Special considerations should be taken for patients with bleeding disorders (i.e. thrombocytopenia)

Reference: Refer to manufacture information. Revised 1/2013
MICU/Respiratory Care

Appendix D

Informed Consent

ORAL MUCOSAL MICROCIRCULATION

Version dated 9/28/2015

RA-2015-305

THE QUEEN'S MEDICAL CENTER
HONOLULU, HAWAII

OCT - 9 2015

INFORMED CONSENT TO TAKE PART IN A CLINICAL RESEARCH STUDY (For Research Subject)

I. Title of Study: Oral Mucosal Microcirculation in the Context of Endotracheal Tube-Related Pressure Ulcer Development

QMC INSTITUTIONAL REVIEW COMMITTEE
DATE 9-9-15
EXPIRES 8-31-16
APPROVED

II. Principle Investigator: Nicolle M. Chun, MS, RN, CCRN
The Queen's Medical Center
T4 MICU
1301 Punchbowl St.
Honolulu, Hi 96813
Phone: 808-691-4141

III. INFORMED CONSENT

You are being asked to take part in this research study that may change how nurses routinely care for patients who are at risk of developing sores in the lips and mouth from a mechanical breathing tube, also called an *endotracheal* tube. We want to learn if moving the breathing tube around the mouth area and giving an area time to rest improves the condition of circulation of blood to the smallest blood vessels of the upper lip and prevents sores. Our goal is to develop a guideline that is based on research, also called *an evidence-based practice*, to prevent mechanical breathing tube related sores in the mouth area.
Before you decide whether or not to take part in this study, you must understand the purpose, how it may help, any risks, and what you have to do. This process is called informed consent. The researchers will talk with you about the study and the informed consent form. The consent also gives you information about what kind of health information will be collected about you as part of the research study and how that information will be used or disclosed by the researchers. Once you understand the study, and if you agree to take part, you will be asked to sign this consent form. If you sign this form you are agreeing to take part in this study and to allow the use and disclosure of your medical records and health information collected in connection with your taking part in this study. You will be given a signed copy to keep. If you do not sign this consent form, you may continue to receive care but not as part of this study.

Before you learn about the study, it is important that you know the following:

- Taking part in this study is of your own free will.
- You may decide not to take part in the study or stop being in the study at any time without it making any difference to your care now or in the future, or to any benefits that you are allowed.

1

- If the study changes in any way which could make a difference to your taking part, you will be told about the changes and may be asked to sign a new consent form.

IV. PURPOSE OF THE STUDY

The purpose of this research study is to describe changes of circulation of blood in the smallest blood vessels in the upper lip of mouth related to the pressure of the mechanical breathing tube. A total of 60 patients receiving care in the Queen's Medical Center (QMC) Medical Intensive Care Unit (MICU) will take part in the study. Your part in the study will last first eight hours of intubation within the MICU. After the described eight hours in the MICU, you will be done with taking part in the study.

V. PROCEDURES

Screening

If you decided to take part in this study, you will be asked to sign this consent form.

When the study begins, a nurse will see if you have a new place to put the tube on your lip that does not have any sores or look like it might develop a sore. This is the spot on your lip that will be examined every two hours for eight hours. To help you understand the procedure, we will call this point A. The nurse will only study Point A as part of this study. But the nurse will also examine your lips every time to determine if you are developing any sores and make sure you receive proper care to help prevent lip and mouth sores.

As part of your routine care, your diagnosis, information about your health status, and laboratory results of blood work will be collected and recorded in your medical record. Although the study will not require any additional tests, we will use this information as part of our study.

When your lip is examined every two hours during the study, you will be helped to sit upright with the head of the bed at a thirty degree angle.

Study Procedures

If there is no sign of skin breakdown and you can use the AnchorFast device, you will be given a random number that only you will have. This random number will help researchers to keep your personal health information collected from taking part in this study from being linked to your identity. Here is a step-by step description of what you can expect:

1. BEGINNING OF THE STUDY: You will already have a breathing tube inserted as part of your regular medical care. When the study starts, the nurse will examine your lip and take a special type of picture of Point A

with a CytoCam, a small wand with a camera that can take images of the circulation of small blood vessels on your lip.

2. Every time a picture is taken with the CytoCam, it will last for four seconds. The nurse will take three pictures each time, and an average of the pictures will be made.
3. The tube will then be moved to Point A on your lip. The tube will remain on Point A for four hours, except when the nurse inspects that spot in two hours. If it looks like you are getting any sores or the tube should be moved sooner for any reason, the nurse will move the tube as your care requires.
4. TWO HOURS: In two hours the nurse will move the tube away from Point A briefly and take another image with the CytoCam and examine the area. Then the nurse will move the tube back to Point A.
5. FOUR HOURS: At four hours the nurse will move the tube from Point A and take an image of Point A using the CytoCam and inspect your lips. The nurse will move the tube to another area on your lip to allow Point A to rest for four hours.
6. SIX HOURS: At six hours the nurse will examine your lip and take a CytoCam image of your lip at Point A.
7. EIGHT HOURS: At eight hours, as the study period is ending, the nurse will examine your lip, take another image of Point A with the CytoCam, examine your lip, and move the tube to another place on your lip.
8. END OF STUDY: A nurse in the MICU will continue monitoring your breathing tube and following routine breathing tube guidelines.

Stopping Your Part in the Study Before the End (Withdrawal or Early Termination)

You can decide to stop being a part of the study at any time. tell your nurse that you no longer wish to take part in the study and no further information will be collected about you.

VI. RISKS

The risks to taking part in this research study are minimal. You will be receiving standard medical and nursing care. The CytoCam device is currently used on newborn babies and adults by researchers at the various hospitals.

VII. BENEFITS

A benefit to participating in this study is that you will be providing information to the researchers that may change the way nurses care for patients who are at risk for mucus membrane breakdown around their mouth area. Also, you should know that there may not be any direct benefit to your participation in the study.

You may choose to not take part in this study without it making a difference in the care that you get now or in the future.

VIII. CONFIDENTIALITY

Federal Privacy Regulations provides Safeguards for privacy, security, and authorized access to health information. The confidentiality of al study-related records will be kept according to all applicable laws. Information gained during this study and information known about you will be kept private to the extent permitted by state and federal law. The results of this research may be presented at meetings or in publication; however, you identity will not be disclosed.

IX. USE AND DISCLOSUE (RELEASE) OF YOUR HEALTH INFORMATION

By signing this form you are authorizing the collection, use and release of your personal health information in medical records and diagnostic imaging and any health information gathered about you as part of this study. Your information will only be used/disclosed as described in this consent form and as permitted by state and federal laws. Your personal health information is health information about you that could be used to identify you. This information may include information about AIDS or HIV infection, treatment for alcohol and/or drug abuse, or mental health or psychiatric services.

The purposes of releasing your protected health information are to collect the data needed to complete the research, to properly monitor (watch) how the study is done, and to answer research questions related to this study.

There is no expiration date to this authorization.

Who may receive, use or release information:
Your medical records and any health information related to this study may be used or released in connection with this research study to the following:

- Nicolle Chun for the purposes of conducting this research study
- The Research and Institutional Review Committee of QMC and staff members of the Research Regulatory Office for purposes of overseeing the research study and making sure that your ethical rights are being protected
- Providers and other healthcare staff of QMC involved in your care

Who may receive the information by the above groups:
The individuals or groups named above may release your medical records, this consent form and the information about you created by this study to:

- The sponsor of this study and their designees
- Federal, state and local agencies having oversight over this research, such as The Office for Human Research Protections in the U.S.

Department of Health and Human Services, and the National Institutes of Health
- Representatives of outside groups hired by QMC Research Department for audits to make sure studies are done as required

There is a possibility that your information may be released again by the sponsor of the study or governmental agencies described above and no longer covered by federal privacy rules.

Right to Withdraw or Stop Taking Part in the Study
You may refuse to sign this authorization. If you refuse to sign the authorization, you will not be able to take part in this study. If you choose not to be in the study, or choose to withdraw from the study, or if you refuse to sign the authorization, it will not make a difference in your usual treatment, or your payment, and it will not change your eligibility for any health plan or health plan benefits that your are allowed.

If you take away your authorization, your part in the study will end and the study staff will stop collecting medical information from you and about you. The researchers and sponsor will continue to use information that has already been collected, but no new information about you will be collected.

Access to Your Information
As is usually the cases, you may see the information in your medical record; however, the records and information related only to the studies that are kept separately will not be available to you until the study is finished. If you wish to review your study records after the completion of the study, you should request this from the study researcher.

X. COSTS

You will not be charged for measuring the blood circulation to the smallest blood vessels in your upper lip with the CytoCam device, no cost to you for moving the breathing tube. All other costs that are part of routine care such will be billed by the Queen's Medical Center as they normally are.

XI. MINIMAL RISK
The research involves minimal risk. If you have an injury or illness as a result of being in this study, immediate emergency medical care and treatment will be given at the usual charge. The investigator and QMC does not have funding (money) set aside to pay for this treatment, lost wages, or other losses resulting from any injury that you may get from taking part in this study.

XII. NEW INFORMATION NEW FINDINGS
You will be told of any important new information learned during the study that may change your willingness to continue in this study.

XIII. REMOVAL FROM THE STUDY

You take part in this study of your own free will. You may be taken off the study without your consent for any of the following reasons:

- Your condition changes and you are no longer able to use the AnchorFast
- Your condition changes and you can no longer be intubated
- Your condition changes and you are no longer able to sitting up right with head of bed 30 degrees
- You are moved from MICU to another unit or other care service teams

IX. WHO TO CONTACT

If you have any questions about your participation in this study, your rights as a volunteer or any other endotracheal tube repositioning and CytoCam relating to this study, you may call Nicolle Chun at (808) 691-4141 and talk about any questions that you might have.

If you cannot get satisfactory answers to your questions or your have comments or complaints about your treatment in this study, you may contact:

Research & Institutional Review Committee
The Queen's Medical Center
1301 Punchbowl Street
Honolulu, HI 96813
Phone: (808) 691-4512

Version dated 9/28/2015

AGREEMENT TO TAKE PART AND CERTIFICATION AND ***AUTHORIZATION OF PROTECTED HEALTH INFORMATION-*** RA-2015-305

I, or my legally authorize representative (the legal person who cares for me) have read and understand the description of this study such as the purpose and nature of this study, its expected length, the procedures to be done, reasonably known risks and discomforts, benefits to expect, other treatment I may have, release of my medical records, payment and medical treatment for injury, and removal without my consent for this research study.

I am taking part in this study of my own free will. I may withdraw (stop taking part) and/or withdraw my authorization for use and release of protected health information at any time after signing this consent form without it making a difference to my care now or in the future or any loss of benefits that I am allowed. My consent does not take away my legal rights in case of carelessness or negligence of anyone connected with this study. My signature means that I have read the information above or that it has been read to me, my questions have been satisfactorily answered, and at anytime I have other questions, I can contact the researcher listed on the first page.

Specially Protected Health Information

I agree to the release of the following information should it be contained in my medical records: Acquired Immune Deficiency Syndrome (AIDS or HIV), alcohol and/or drug abuse treatment, or behavioral or mental health services.

OMC INSTITUTIONAL REVIEW COMMITTEE
DATE 9-9-15
EXPIRES 8-31-16
APPROVED

cc: ***Signed copy*** of consent/authorization from to patient

Subject's Name (Print)	Subject's Signature	Date/Time
Witness' Name (Print) (Witnessing Signature Only)	Witness' Signature **********	Date/Time

I have explained this research to the above subject. In my judgment the subject is voluntarily and knowingly giving informed consent and has the legal capacity to give informed consent to take part in this research study.

Investigator's Name (Print) (Individual obtaining Subject's consent)	Investigator's Signature	Date/Time

(Investigator: fax a copy of this signed page to Research Regulatory Office at 691-7897 within 24 hours of signing.)

RA-2015-305

CONSENT TO TAKE PART and ***AUTHORIZATION OF PROTECTED HEALTH INFORMATION*** **– IF SUBJECT IS UNABLE TO CONSENT:**

As a legally authorized representative of the subject, my signature indicates that I have read this form, or it has been read to me, I have had the study explained to me, I have had answers to my questions, and I am satisfied with the information that I have been given. I am giving consent for the subject listed below to take part in this study and authorize the use and release of their protected health information. I can withdraw (stop taking part) and or take away the authorization for the use and release of protected health information at any time after signing this for without it making a difference to the subject's care now or in the future or any loss of benefits that I am allowed. My consent does not take away legal rights in care of carelessness or negligence of anyone connected with this study. I will be given a signed copy of this consent form.

Specially Protected Health Information

I agree to the release of the following information if it is in the subject's medical records: Acquired Immune Deficiency Syndrome (AIDS or HIV), alcohol and/or drug abuse treatment, or behavioral or mental health services.

_____ is not able to consent
Name of the Subject (Print)

_____ _____
Name of Legal Representative (Print) Signature of Legal Representative

_____ _____
Description of legal authority to act on behalf of subject Date/Time

_____ _____ _____
Witness' Name (Print) Witness' Signature Date/Time
(Witness Signature only) **********

Based on my clinical judgment, this subject is not able or is incompetent to independently consent to participate in this research study.

_____ _____ _____
Investigator's Name (Print) Investigator's Signature Date/Time
(Individual obtaining the Legally Authorized Representative's consent)

(Investigator: Fax a copy of this signed page to Research Regulatory Office at 691-7897 within 24 hours of signing.)

Appendix E

Data Recording Sheets

QMC Study: ORAL MUCOSAL MICROCIRCULATION 47
Version dated: 9/28/2015

Appendix 6. Data Collection Sheet RA-2015-305

ID [#]:						
Age [yrs]:						
Admiss. Date [mm-dd-yyyy]:						
Admiss. Time [hh:mm]:						
Intubat. Date [mm-dd-yyyy]:						
Intubat. Time [hh:mm]:						
Size of ETT:						
	Initial Area 1 (Baseline)	2h post ETT Area 1	4h post ETT Area 1	2h free ETT Area 1	4h Free ETT Area 1	Comment
Time [hh:mm]:						
Body Temp. [°F]:						
HR [bpm]:						
Systolic BP [mmHg]:						
Diastolic BP [mmHg]:						
MAP [mmHg]:						
Anticoagulants						
Braden Scale Score [1-12]:						
SOFA Score [1/2/3/4]:						
Microcirculation Variables						
TCD [cpll/mm^2]:						
FCD [cpll/mm^2]:						
PPC [%]:						
BVd *[μ]:*						
MFI [0/1/2/3]:						

QMC INSTITUTIONAL REVIEW COMMITTEE
DATE 9-9-15
EXPIRES 8-31-16
APPROVED

OCT - 9 2015

Appendix F

BRADEN SCALE FOR PREDICTING PRESSURE SORE RISK

Patient's Name _____ Evaluator's Name _____ Date of Assessment

SENSORY PERCEPTION ability to respond meaningfully to pressure-related discomfort	**1. Completely Limited** Unresponsive (does not moan, flinch, or grasp) to painful stimuli, due to diminished level of consciousness or sedation. OR limited ability to feel pain over most of body	**2. Very Limited** Responds only to painful stimuli. Cannot communicate discomfort except by moaning or restlessness OR has a sensory impairment which limits the ability to feel pain or discomfort over ½ of body.	**3. Slightly Limited** Responds to verbal commands, but cannot always communicate discomfort or the need to be turned. OR has some sensory impairment which limits ability to feel pain or discomfort in 1 or 2 extremities.	**4. No Impairment** Responds to verbal commands. Has no sensory deficit which would limit ability to feel or voice pain or discomfort..				
MOISTURE degree to which skin is exposed to moisture	**1. Constantly Moist** Skin is kept moist almost constantly by perspiration, urine, etc. Dampness is detected every time patient is moved or turned.	**2. Very Moist** Skin is often, but not always moist. Linen must be changed at least once a shift.	**3. Occasionally Moist:** Skin is occasionally moist, requiring an extra linen change approximately once a day.	**4. Rarely Moist** Skin is usually dry, linen only requires changing at routine intervals.				
ACTIVITY degree of physical activity	**1. Bedfast** Confined to bed.	**2. Chairfast** Ability to walk severely limited or non-existent. Cannot bear own weight and/or must be assisted into chair or wheelchair.	**3. Walks Occasionally** Walks occasionally during day, but for very short distances, with or without assistance. Spends majority of each shift in bed or chair	**4. Walks Frequently** Walks outside room at least twice a day and inside room at least once every two hours during waking hours				
MOBILITY ability to change and control body position	**1. Completely Immobile** Does not make even slight changes in body or extremity position without assistance	**2. Very Limited** Makes occasional slight changes in body or extremity position but unable to make frequent or significant changes independently.	**3. Slightly Limited** Makes frequent though slight changes in body or extremity position independently.	**4. No Limitation** Makes major and frequent changes in position without assistance.				
NUTRITION usual food intake pattern	**1. Very Poor** Never eats a complete meal. Rarely eats more than ⅓ of any food offered. Eats 2 servings or less of protein (meat or dairy products) per day. Takes fluids poorly. Does not take a liquid dietary supplement OR is NPO and/or maintained on clear liquids or IV's for more than 5 days.	**2. Probably Inadequate** Rarely eats a complete meal and generally eats only about ½ of any food offered. Protein intake includes only 3 servings of meat or dairy products per day. Occasionally will take a dietary supplement. OR receives less than optimum amount of liquid diet or tube feeding	**3. Adequate** Eats over half of most meals. Eats a total of 4 servings of protein (meat, dairy products per day. Occasionally will refuse a meal, but will usually take a supplement when offered OR is on a tube feeding or TPN regimen which probably meets most of nutritional needs	**4. Excellent** Eats most of every meal. Never refuses a meal. Usually eats a total of 4 or more servings of meat and dairy products. Occasionally eats between meals. Does not require supplementation.				
FRICTION & SHEAR	**1. Problem** Requires moderate to maximum assistance in moving. Complete lifting without sliding against sheets is impossible. Frequently slides down in bed or chair, requiring frequent repositioning with maximum assistance. Spasticity, contractures or agitation leads to almost constant friction	**2. Potential Problem** Moves feebly or requires minimum assistance. During a move skin probably slides to some extent against sheets, chair, restraints or other devices. Maintains relatively good position in chair or bed most of the time but occasionally slides down.	**3. No Apparent Problem** Moves in bed and in chair independently and has sufficient muscle strength to lift up completely during move. Maintains good position in bed or chair.					
				Total Score				

Reprinted with permission.

References

Anatomy of the lips, mouth, and oral region. (2015, March 6). Retrieved from http://elementsofmorphology.nih.gov/anatomy-oral.shtml.

Arts, D., de Keizer, N., Vroom, M. & de Jonge, E. (2005). Reliability and accuracy of Sequential Organ Failure Assessment (SOFA) scoring. *Critical Care Medicine, 33* (9), 1988-1993.

Apold, J., &Rydrych, D. (2012). Preventing device-related pressure ulcers: using data to guide statewide change. *Journal of Nursing Care Quality*, *27*(1), 28-34.doi: 10.1097/NCQ.0b013e31822b1fd9

Aykut, G., Ince, Y. & Ince, C. (2014). A New Generation Computer-controlled Imaging Sensor-based Hand-held Microscope for Quantifying Bedside Microcirculatory Alterations. In J.-L. Vincent (Ed.), Annual Update in Intensive Care and Emergency Medicine 2014 (Vol. 2014, pp. 367-381): Springer International Publishing.

Aykut, G., Veenstra, G., Scorcella, C, Ince, C. & Boerma, C. (2015). Cytocam-IDF (incident dark field illumination) imaging for bedside monitoring of the microcirculation.*Intensive Care Medicine Experimental*, *3*(4), 1-10.doi: 10.1186/s40635-015-0040-7.

Berlowitz, D., Lukas, C. V., Parker, V., Niederhauser, A., Silver, J., Loga, C., Ayello, E. & Zulkowski, K. (2014). Preventing pressure ulcers in hospitals. Retrieved from http://www.ahrq.gov/professionals/systems/hospital/pressureulcertoolkit/

Black, J. M., Cuddigan, J. E., Walko, M. A., Didier, L. A., Lander, M. J., & Kelpe, M. R. (2010). Medical device related pressure ulcers in hospitalized patients. *International Wound Journal*, *7*(5), 358-365.doi: 10.1111/j.1742-481X.2010.00699.x

Bergstrom, N. & Braden, B. (1992). A prospective study of pressure sore risk among institutionalized elderly. *Journal of the American Geriatrics Society*, *40*(8), 747-758.

Braden, B. & Bergstrom, N. (1988). Braden scale for predicting pressure sore risk. Retrieved from http://www.bradenscale.com/images/bradenscale.pdf.

Boerma, E., Mathura K., van der Voort, P.,Spronk, P. & Ince, C. (2005). Quantifying bedside-derived imaging of microcirculatory abnormalities in septic patients: a prospective validation study. Critical Care. *9(6),* R601-6.

Chun, N. (2014). *Probable variables affecting device-related oral mucosa pressure ulcers at the Queen's Medical Center Medical Intensive Care Unit.* Unpublished manuscript.

Cooper, K. (2013). Evidence-based prevention of pressure ulcers in the intensive care unit. Critical Care Nurse, *33(6),* 57-66.

Coyer, F. M., Stotts, N. A., & Blackman, V. S. (2014). A prospective window into medical device-related pressure ulcers in intensive care. *International Wound Journal*, *11*(6), 656-664. Blackwell Publishing Ltd.

CytoCam. (2015, March 6). Retrieved from http://www.braedius.com/magnoliaPublic/braedius/products/cytoCam.html.

De Backer D, Creteur J, Preiser JC, et al. (2002). Microvascular blood flow is altered in patients with sepsis. *American Journal of Respir and Care Med*. 2002, *166(1),*98-104.

De Backer, D., Hollenberg, S., Boerma, C., Goedhart, P., Buchele, G., Ospina-Tascon, G., & Ince, C. (2007). How to evaluate the microcirculation: Report of a round table conference. *Critical Care, 11*(5), R101. doi: 10.1186/cc6118.

Defloor, T. (1999). The risk of pressure sores: a conceptual scheme. *Journal of Clinical Nursing, 8(2),* 206-216.

Dirkes M.C., Milstein, D.M.J., Heger, M, & van Gulik, T.M. (2015). Absence of hydrogen sulfide-induced hypometabolism in pigs: a mechanistic explanation in relation to small non-hibernating mammals. European Surgical Research, *54(3-4),* 178-91.

Djaberi, R., Schuijf, J., Koning, E., Wijewickrama, D., Pereira, A., Smit, J.,…. Jukema, J. (2012). Non-invasive assessment of microcirculation by sidestream dark field imaging as a marker of coronary artery disease in diabetes. *Diabetes & Vascular Diseas Research, 10(2),* 123-134.

Gogos, C., Lekkou, A., Papageorgious, O., Siagris, D., Skoutelis, A. & Bassaris, H. (2003). Clinical prognostic markers in patients with severe sepsis: A prospective analysis of 139 consecutive cases. *Journal of Infection, 47*(4), 300-306.

Ferreira, F. L., Bota, D. P., Bross, A., Melot, C., & Vincent, J. L. (2001). Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA, 286*(14), 1754-1758.

Fisher, D., Chennel, C., Marchese, A., Kratohvil, J. & Kacmarek, R. (2014). Comparison of commercial and noncommercial endotracheal tube-securing devices. *Respiratory Care, 59(9),* 1-9.

Fletcher J. (2012). Device related pressure ulcers made easy. *Wounds UK*. *8*(2). 1-4.

Halfens, R., Van Achterberg, T. & Bal, R. (2000). Validity and reliability of the Braden scale and the influence of other risk factors: A multi-centre prospective study. *International Journal of Nursing Studies*, *37*(4), 313-319.

Hanonu, S., & Karadag, A. (2016). A Prospective, Descriptive Study to Determine the Rate and Characteristics of and Risk Factors for the Development of Medical Device-related Pressure Ulcers in Intensive Care Units. *Ostomy/wound management*, *62*(2), 12-22. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/26901386

Haessler, E. (2014). National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance. Prevention and Treatment of Pressure Ulcers: Quick Reference Guide. Osborne Park, Australia: Cambridge Media.

Heckmann, J. G., Hilz, M. J., Hummel, T., Popp, M., Marthol, H., Neundorfer, B., & Heckmann, S. M. (2000). Oral mucosal blood flow following dry ice stimulation in humans. *Clinical Autonomic Research*, *10*(5), 317-321.

How it works/CytoCam-IDF. (2015, March 6). Retrieved from http://www.braedius.com/magnoliaPublic/braedius/products/cytoCam.html.

Hyzy, R. (2017). Complications of the endotracheal tube following initial placement: prevention and management in adult intensive care unit patients. Retrieved from https://www.uptodate.com/contents/complications-of-the-endotracheal-tube-following-initial-placement-prevention-and-management-in-adult-intensive-care-unit-patients, retrieved on 7/5/2018).

Jones, A., Trzeciak, S. & Kline, J. (2009). The sequential organ failure assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. *Critical Care Medicine*, *37*(5), 1649-1654.doi: 10.1097/CCM.0b013e31819def97

Kaplow, R. & Bookbinder, M. (1994). A comparison of four endotracheal tube holders. *Heart & Lung: The Journal of Critical Care, 23(1),* 59-66.

Keller, B., Wille, J., Ramshorst, B.V. & Werken, C. V. D. (2002). Pressure ulcers in intensive care patients: A review of risks and prevention. *Intensive Care Medicine.28*, 1379-1388.doi: 10.1007/s00134-002-1487-z

Kring, D. (2007). Reliability and validity of the Braden Scale for predicting pressure ulcer risk. *Journal of Wound, Ostomyand Continence Nurses.34*, 399-406.

Labial mucosa. (2015, March 6). Retrieved from http://medical-dictionary.thefreedictionary.com/labial+mucosa.

Levinson, A., Casserly, B. & Levy, M. (2011). Reducing mortality in severe sepsis and septic shock. *Seminars in Respiratory and Critical Care Medicine, 32*(2), 195-205.

Lindeboom, J., Mathura, K, Ramsoekh, D., Harkisoen, S., Aartman, I., van den Akker, H., Ince, C. (2006). The assessment of the gingival capillary density with orthogonal polarization spectral (OPS) imaging. Archives of Oral Biology, 51(8), 697-702.

Liu, J., Zhang, S., Gong, W., Li, S., Wang, F….Hang, Y. (2010). Correlations between controlled endotracheal tube cuff pressure and postprocedural complications: a multicentere study. *Anesthesia & Analgesia, 111(5),* 1133-1137.

Lipowsky, H. (2005). Microvascular rheology and hemodynamics. *Microcirculation, 12(1),* 5-15.

Madhav, N. & Ojha, A. (2012). Labial mucosa as a novel transcmucosal drug delivery platform. *International Journal of Pharmacy and Pharmaceutical Sciences, 4(3),* 83-90.

Medina, E., Milstein, D. M. J., & Ince, C. (2014). Monitoring the Microcirculation in Critically Ill Patients. In J. M. Ehrenfeld & M. Cannesson (Eds.), Monitoring Technologies in Acute Care Environments (pp. 127-136): Springer New York.

Microcirculation. (n.d.) *Medical Dictionary for the Health Professions and Nursing*. (2012). Retrieved April 21, 2015 from http://medical-dictionary.thefreedictionary.com/microcirculation

Milstien, D., van Kuijen, A., Copper, M., Karakullukçu, B., Tan, I., Lindeboom, J…. Ince C.(2012). Monitoring microcirculatory alterations in oral squamous cell carcinoma following photodynamic therapy. Photodiagnosis Photodynamic Therapy. *9(1),* 69-75.

Nakagawa, K. Sakurai, K., Ueda-Kodaira, Y. & Ueda, T. (2010). Age-related changes in elastic properties and moisture content of lower labial mucosa. Journal of Oral Rehabilitation; 38(4): 235-241.

National Pressure Ulcer Advisory Panel. Mucosal pressure ulcers: an NPUAP position statement. 2011. http://www.npaup.org/position.htm. Accessed November 2, 2011.

Nolte, D., Zeintl, H., Steinbauer, M., Pickelmann, S., Messmer, K. (1995). Functional capillary density: an indicator of tissue perfusion? International Journal of Microcirculation, Clinical and Experimental, *15(5),* 244-9.

Norman, J. (2013, June). MDRPressure Ulcers: Who thought plastic tubeing could be harmful? *Healthy Skin*. Retrieved from https://www.medlineuniversity.com/DesktopModules/Documents/ViewDocument.aspx?AddToLog=1&DocumentID=1390

Oral mucosa. (2015, January 5). Retrived March 1, 2016, from https://pocketdentistry.com/9-oral-mucosa/

Ozyurek, P., & Yavuz, M. (2015). Prevention of pressure ulcers in the intensive care unit: a randomized trial of 2 viscoelastic foam support surfaces. Clinical nurse specialist CNS, 29(4), 210-7.

Petersen, S. M., Greisen, G., Hyttel-Sorensen, S., & Hahn, G. H. (2014). Sidestream dark field images of the microcirculation: intra-observer reliability and correlation between two semi-quantitative methods for determining flow. *BMC Med Imaging*, 14, 14. doi: 10.1186/1471-2342-14-14.

Sakr, Y., Dubois, M., De Backer, D., Creteur, J. & Vincent, J. (2004). Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. *Critical Care Med, 32(9),*1825-31.

Salcido, R., Popescu, A. & Ahn, C. (2007). Animal models in pressure ulcer research, Journal of Spinal Cord Medication, *30(2),* 107-116.

Scardina, G., Ruggieri, A., & Messina, P. (2009). Evaluation of labial microvessels in Sjogren syndrome: A videocapillaroscopic study. *Annals of Anatomy*, 191(3): 273-279.

Scardina, G., Pisano, T., Carini, F, Valenza, V. & Messina, P. (2008). Burning mouth syndrome. *The Journal of the American Dental Association*, 139(7), 940-946.

Sherman H, Klausner S, Cook WA. (1971). Incident dark-field illumination: a new method for microcirculatory study. Angiology, *22(5),* 295-303.

Slaaf, D., Tangelder, G., Reneman, R., Jager, K., Bollinger, A. (1987). A versatile incident illuminator for intravital microscopy. International Journal of Microcirculation, Clinical and Experimental, *6(4),* 391-397.

Sonis, S. (2004). The pathobiology of mucositis. Nature Reviews Cancer, 4, 277-284. doi:0.1038/nrc1318.

http://www.nature.com/nrc/journal/v4/n4/fig_tab/nrc1318_F1.html#close. Accessed April 15, 2015.

Tayyib, N., Coyer, F., & Lewis, P. (2013). Pressure ulcers in the adult intensive care unit: a literature review of patient risk factors and risk assessment scales. Journal of Nursing Education and Practice, 3(11). doi https://doi.org/10.5430/jnep.v3n11p28

Tsai, A., Friesenecker, B. & Intaglietta, M (1995). Capillary Flow Impairment and Functional Capillary Density. International Journal of Microcirculation, *15*(5), 238-243.

Trzeciak, S., Cinel, I., Dellinger, P., Shapiro, N., Arnold, R., Parrillo, J., & Hollenberg, S. (2008). Resuscitating the microcirculation in sepsis: The central role of nitric oxide, emerging concepts for novel therapies, and challenges for clinical trials. *Academic Emergency Medicine,15*(5), 399-413.doi:10.1111/j.1553-2712.2008.00109.x.

Trzeciak, S., Dellinger, P., Parrillo, J., Guglielmi, M., Bajaj, J., Abate, N…Hollenberg, S. (2007). Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival. Annals of Emergency Medicine, *49*(1), 88-98, 98 e81-82. doi: 10.1016/j.annemergmed.2006.08.021

Tsuji, S., Ishioka, S., Sekiya, N., & Nakatsuka, T. (2005). Analysis of ischemia-reperfusion injury in a microcirculatory model of pressure ulcers. *Wound Repair & Regeneration*, 13, 209-215.

Tytgat, S., van der Zee, D., Ince, C. & Milstein, D. (2013). Carbon dioxide gas pneumoperitoneum induces minimal microcirculatory changes in neonates during laparoscopic pyloromyotomy. Surgical Endoscopy, *27(9)*, 3465-73.

Vincent, J., de Mendonca, A., Cantraine, F., Moreno, R., Takala, J., Suter, P., Blecher, S. (1998). Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. Critical Care Medicine, *26(11)*, 1793-1800.

Weber, M., Milstein, D., Ince, C., Rengerink, K. &Roovers, J. (2014). Vaginal microcirculation: Non-Invasive anatomical examination of the micro-vessel architecture, tortuosity and capillary density. *Neurourology and Urodynamics*, 1-7. doi: 10.1002/nau22662.

Woodrow, P., Elliott, J., & Beldon, P. (2013). Assessment and care of tissue viability, and mouth and eye hygiene needs. In Mallett, J., Albarran, J., & Richardson, A (Eds.), *Critical Care Manual of Clinical Procedures and Competencies* (2047-2059). West Sussex, UK: Wiley-Blackwell.

Yamashita, M., Nishio, A., Daizo, H., Kishibe, M. & Shimada, K. (2014). Intraooperative acquired pressure ulcer on lower lip: a complication of rhinoplasty. *Journal of Craniofacial Surgery. 25(1).* e3-e4.

Yu, Q., Pang, K., Ran, W., Phillipsen, H. & Chen, X. (1994). The microvasculature of human infant oral mucosa using vascular corrosion casts and India ink injection. II. Palate and lip. Scanning Microscopy, 8, 133-139.

Zakatkiewicz, S., Teegardin, C. & Whitney, J. (2012). Retrospective review of the reduction

of oral pressure ulcers in mechanically ventilated patients. Critical Care Nursing Quarterly, *35(3)*, 247-254

Zygun, D., Berthiaume, L., Laupland, K., Kortbeek, J. & Doig, C. (2006). SOFA is superior to MOD score for the determination of non-neurologic organ dysfunction in patients with severe traumatic brain injury: a cohort study. *Critical Care, 10*, 1-10.doi:10.1186/cc5007